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A COMPARATIVE SURVEY

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ANIMAL HORMONES

A comparative survey

Part I—Kinetic and Metabolic Hormones

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CONTENTS

PAGE
List of Tables vii
Acknowledgements ix
Preface xiii
CHAPTER
1 Introduction 1
1.1 Discovery of Hormones 1
1.2 Chemical Activators 2
1.3 Mechanical Activation 4
1.4 Definitions of Hormones 5
1.5 Types of Hormones 6
1.51 Kinetic hormones 9
1.52 Metabolic hormones 10
1.53 Morphogenetic hormones 11
1.6 Identification 12
1.7 References 16

2 Sources of Kinetic and Metabolic Hormones 18
2.1 Ectodermal Sources 18
2.11 Secretory cells derived from the nervous system 19
2.12 Endocrine glands derived from ectodermal epithelium 38
2.2 Endodermal Sources in Vertebrata 44
2.21 Isolated cells in the gut 44
2.22 Endodermal endocrine glands 46
2.3 Mesodermal Sources in Vertebrata 50
2.31 Endocrine gland cells derived from coelomic epithelium 50
2.4 References 53

3 Kinetic Hormones—I. Control of Muscles and Pigmentary Effectors 56
3.1 Control of Muscles 57
3.11 Visceral muscle 57
3.12 Somatic muscles 69
3.2 Control of Pigmentary Effectors 70
3.21 Chromatophores with muscles 72
3.22 Pigmentary effectors with movable pigment granules 73
3.3 References 110

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CHAPTER PAGE

4 KINETIC HORMONES—II. CONTROL OF EXOCRINE AND ENDOCRINE GLANDS 115
4.1 Exocrine Glands 115
4.11 Digestive glands 117
4.12 Oviducal glands 128
4.13 Milk-secreting glands 130
4.14 Skin glands 131
4.2 Endocrine Glands 131
4.21 Ectodermal endocrine glands of Arthropoda 134
4.22 Endodermal endocrine glands of Vertebrata 139
4.23 Mesodermal endocrine glands of Vertebrata 143
4.3 General Considerations 152
4.31 Characteristics of kinetic hormones 152
4.32 Stimulation of the secretion of kinetic hormones 155
4.4 References 163

5 METABOLIC HORMONES 167
5.1 General Metabolic Rate 168
5.11 Respiration 168
5.12 Fat metabolism 186
5.2 Intermediary Metabolism of Carbohydrates and Proteins 189
5.21 Carbohydrate metabolism 189
5.22 Protein metabolism 199
5.3 Balance of Monovalent Electrolytes and Water 206
5.31 Balance of sodium ions (Na^+) and of associated monovalent electrolytes (K^+ and Cl^-) 209
5.32 Water balance 219
5.4 Balance of Calcium and Phosphates 240
5.41 Balance of calcium 240
5.42 Balance of phosphates 249
5.5 General Considerations 252
5.51 Characteristics of the metabolic hormones 252
5.52 Control of the secretion of metabolic hormones 253
5.53 Hormones and the environment 259
5.6 References 260

GLOSSARY 267

INDEX OF AUTHORS 271

INDEX OF ANIMAL NAMES 277

INDEX OF SUBJECTS 283

LIST OF TABLES

TABLE PAGE

1 Summary of the Main Types of Action of Vascular Hormones 8
2 Steps in Establishing Direct and Indirect Actions of Two Interacting Hormones 14
3 Ectodermal Sources of Kinetic and Metabolic Hormones 22
4 Cells in the Pars Distalis of the Adenohypophysis 44
5 Endodermal Sources of Kinetic and Metabolic Hormones in Vertebrata 46
6 Mesodermal Sources of Metabolic Hormones in Vertebrata 51
7 Kinetic Hormones Controlling Muscles 58
8 Kinetic Hormones Controlling Pigmentary Effectors 71
9 Kinetic Hormones Controlling Chromatophores with Movable Pigment 87
10 Crustacean Hormones Controlling White Pigment in Relation to Light 96
11 Crustacean Hormones Controlling Red and Black Pigments in Chromatophores in Relation to Light 98
12 Changes in Melanophore Index in *Ligia* 100
13 Illumination of Different Areas of the Eyes of *Ligia* 102
14 Kinetic Hormones Controlling Exocrine Glands in the Gut 118
15 Kinetic Hormones Controlling other Exocrine Glands 129
16 Endocrinokinetic Hormones Stimulating Endocrine Glands 133

TABLE		PAGE
17	Means of Controlling the Secretion of Kinetic Hormones	156–157
18	Metabolic Hormones Controlling Respiration and Fats	169
19	Changes in Oxygen Consumption in *Astacus*, following Sinus Gland or Eyestalk Removal	179
20	Changes in Fat Content of the Body of Crabs (*Hemigrapsus nudus*) following Starvation and Sinus Gland Removal	188
21	Metabolic Hormones Controlling Carbohydrates and Proteins	190
22	The Effect of Asphyxia on the Concentration of Blood-Sugar	192
23	Changes in Body Composition of Crabs (*Hemigrapsus nudus*) following Starvation and Sinus Gland Removal	200
24	Hormones Associated with Nitrogen Excretion in Crabs	204
25	Metabolic Hormones Controlling Electrolytes and Water	208
26	Changes in Sodium and Potassium Concentration of Plasma and Muscle, following Adrenalectomy	217
27	Changes in Excretion of Water, Sodium and Potassium, following Adrenalectomy	229
28	Metabolic Hormones Controlling the Balance of Calcium and Phosphates	241
29	Effect on Blood Calcium of Injection of Hypophysial Hormones into *Xenopus*	245
30	Changes in the Calcium Content of the Blood of the Crayfish (*Astacus*), following Removal of either the Sinus Glands or the Whole Eyestalks	248
31	Means of Controlling the Secretion of Metabolic Hormones	254–255

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This book
is
dedicated
to my Students,
who, by their questions,
have stimulated me
to write it

FOREWORD

A foreword, like an aperitif, should whet the appetite without dulling the critical appreciation of what is to follow. Many wise people therefore avoid them. Nevertheless, it is a personal pleasure for me to be asked to provide one to this volume, for the initiation of which I was, at least in part, responsible.

Specialized scientific publications in these days may be broadly, and thus inaccurately, divided into scientific papers summarizing experiments, reviews summarizing scientific papers, and books summarizing reviews. Among the multitude of these last, the really interesting book is all too rare—one with a broad but scholarly treatment, which stimulates the reader to think about the subject, to produce his own ideas and to design his own experiments. Such a book must provide a sufficiently clear account of the experimental techniques for the student to appreciate the methods of study and their limitations; it must establish a theoretical background which gives coherence to the subject as a whole; finally it must tread sufficiently near to the frontiers of knowledge to provide a glimpse of what may lie beyond.

Such a stimulus has already reached several generations of Bristol students through Dr. Jenkin's lectures on hormones; I hope that in its present form her book will successfully challenge a wider audience.

John E. Harris

PREFACE

THE IDEA of writing this book arose from lecturing on hormones to second and third year students of zoology, for whom the subject formed part of a course in comparative physiology. It was found that no introductory book covered the whole subject equally; even Hanström's admirable *Hormones in Invertebrates* (1939) dealt with only a part of the field and was already out of date in 1956, when he assured me that he would not be rewriting it and encouraged me to attempt this general survey.

To do so necessitated evolving a scheme within which to consider and select suitable examples from the mass of available material. This resulted in a comparative arrangement, which should be of general application, since it is based on the actions of hormones, rather than on their sources or on their phyletic distribution.

The actions of hormones were then seen to fall into three well-defined groups, the *kinetic*, the *metabolic* and the *morphogenetic*, although these had not all been named nor clearly defined at that time. Subdividing these groups brought together examples acting upon similar effectors, such as muscles, chromatophores or glands, or having similar metabolic actions, such as increasing water excretion, blood-sugar or respiration. Still further subdivision brought together the hormones that stimulate a given action or facilitate a given process and separated them from those having the opposite effects. When consistently adhered to, this approach helped to give a clear picture of hormone actions, to emphasize cases where antagonistic hormones were known and to draw attention to apparent gaps in recorded knowledge.

In writing the book, invertebrates and vertebrates were placed side by side to show the extent to which both are now known to have hormones with similar actions. Describing the invertebrate examples before those from vertebrates was a deliberate attempt to emphasize this fact. To have given pride of place to the vertebrates might have given a more clear-cut picture, and could certainly have provided more abundant and detailed examples; but it would have thrown the intended comparison out of perspective. The search for good examples among invertebrates proved unexpectedly successful. It has been decided, therefore, to publish the book in two parts instead of one; but the unified plan of relatively simple presentation is being maintained.

The present part of the book covers only the kinetic and metabolic hormones, their sources, actions and the ways in which their secretion is controlled. The second part* will contain a similar treatment of the morphogenetic hormones, namely those concerned with growth, differentiation and reproduction; it will also discuss such topics as the relation of the chemical constitution of hormones to the sources from which they are derived and their type of action. A consideration of the distribution of hormones in the animal kingdom may also throw some light on the possible evolution of these chemical activators, as well as suggesting problems for investigation.

Many of these problems must be apparent to anyone who surveys the field of hormone research; yet it is permissible to assume that few research workers have time to undertake such a survey, as their own work becomes more and more specialized and results in the publication of books that are confined to single classes of animals or single endocrine organs. It is therefore hoped that the present work may be useful to some specialists as well as to the teachers and students for whom it is primarily intended.

It has clearly not been possible for the writer to review the whole literature of so rapidly expanding a subject; but the main original papers on the kinetic and metabolic hormones of invertebrates have been covered up to the summer of 1958, while the vertebrate examples have been checked by recent reviews and reports of symposia. The references at the end of each chapter show the sources used, but make no pretence to being complete, though they should provide a useful starting point for anyone wishing to go further.

---

* *Animal Hormones,* a comparative survey. Part II. *Morphogenetic Hormones,* in preparation.

It is much to be regretted that these references are not more nearly up to date; but publication has been delayed by various unforeseeable causes, including the printing industry's national dispute during 1959 and the writer's serious illness.

Finally a word of explanation about some of the things which have not been included in the book. Examples in which extracts of one kind of animal have been tested upon another kind have been avoided, on the grounds that they are apt to lead to unsound physiological deductions. Details of standard techniques are omitted, since the reader can refer to any physiological textbook for an account of such methods as recording muscle contractions by means of levers that mark a revolving smoked drum (e.g. Figs. 3-1 and 3-3). The use of commercial hormone preparations and methods of quantitative estimation of hormones by biological assay are also omitted, as being primarily of clinical interest. Since the book is intended for zoologists and comparative physiologists, the mammalian examples have been chosen from species other than man, while reference to pathological and clinical material has been omitted, as being outside their chosen field. Such material is easily accessible elsewhere, and should not be difficult to fit into the present framework, if the reader so desires.

Bristol. P. M. J.

CHAPTER 1

INTRODUCTION

1.1 Discovery of hormones

THE DISCOVERY of hormones was a late-comer in the study of physiology; the circulation of the blood was demonstrated in the seventeenth century by Harvey (1628), but it was more than two centuries before it was realized that chemical messengers could be carried in that circulation. The first hint of this was when Berthold (1849)* showed conclusively that the morphogenetic effects of transplanting the testes of cockerels must be transmitted by some factor in the blood. It was even longer before Oliver and Schäfer (1895) found that a chemical extract of the adrenal medulla, if injected into the circulation, could induce a pronounced rise in blood pressure. In 1901 the active substance in this extract was isolated, identified and called ADRENALINE. The general term "Hormone" is derived from the Greek *ὁρμάω*, meaning "I arouse", and indicates the stimulating action of such chemicals; it was first used by Starling (1905) for SECRETIN, that had been discovered in 1902 and shown to induce the flow of alkali from the pancreas. Two hormones concerned with the cure of human disease, INSULIN for the control of diabetes mellitus, and THYROXINE for cretinism, were among the more spectacular discoveries of the early twentieth century, and led to an intensive search for more hormones in man and other mammals. This resulted in the gradual discovery of some thirty kinds of endocrine cells and glands that can produce minute quantities of chemical substances which are carried in the blood, to stimulate or inhibit various specific effectors, or to control different aspects of metabolism and morphogenesis.

---

* See Harris (1955) for a translated account of his experiments.

The first indication of any hormone in an invertebrate was that postulated by Kopeć (1922) as carrying the brain stimulus for moulting in *Lymantria*. Then Koller (1927) found a blood-borne factor controlling the colour changes of certain shrimps, and Perkins (1928) located its source in the eyestalk. The discovery of other hormones has followed, mainly in crustaceans and insects, where they have almost as many actions as those carried out by the better-known hormones of vertebrates.

1.2 CHEMICAL ACTIVATORS

During this period, when hormones were being discovered in ever-increasing numbers, different kinds of chemical activators were being found in other fields of biology. Substances akin to hormones were found in plants; nerve transmission in vertebrates and some invertebrates was found in many unrelated species to be due to release of either acetylcholine or adrenaline, at the point of contact between one neuron and the next, or between the motor axon and its effector. The control of the pattern of development in early embryos of Amphibia was found to be due to the diffusion from cell to cell of particular chemical substances or organizers; these substances were not specific in that they were capable of producing similar effects in a wide range of genera (Spemann and Mangold, 1924).

Some order was brought into the variety and diversity of these and other chemical activators by Huxley (1935) in an important scheme of classification. Its main weakness was that it did not include neurosecretory cells derived from nerve cells and capable of yielding hormones. These cells had been recognized histologically in vertebrates by Dahlgren (1914), and in some invertebrates by Hanström (1931); but their action in releasing hormone-like substances into the blood was first established by the Scharrers (1937). They are now well known in Annelida, Arthropoda and some other invertebrates as well as in vertebrates.

Huxley's (1935) classification of chemical activators may therefore be modified as follows, to include neurosecretion:

A. PARA-ACTIVATORS. By-products of normal and pathological metabolism with effects on correlation or differentiation, e.g. carbon dioxide in its effect on the respiratory centre.

B. True Activators. Chemical substances produced by the organism and exerting specific functions in regard to correlation or differentiation:

1. *Local activators*, with effects on the same cell, or cells, within which they are produced.
    - (a) *Intracellular activators* ("intracellular hormones" of Goldschmidt), acting in each cell singly and being the direct expression of *gene* activity, in relation to regional differentiation.
    - (b) *Regional activators*, responsible for the *chemodifferentiation* of specific regions in embryos and for *growth gradients*.
2. *Distance activators*, with effects on cells other than those in which they are produced.
    - (a) *Diffusion activators*, distributed by diffusion through the tissues.
        - (i) Direction of transport restricted by structural organization. *Growth hormones* in *plants*.
        - (ii) Diffusion restricted to tissues in direct contact. *Organizers* in embryos and "*organisines*" in animals without a circulatory system. It is possible that the cortical releasing factor, *CRF*, from the brain of vertebrates should also be included here (§ 4.323).
        - (iii) Diffusion restricted mainly by chemical means. *Neurohumoral secretions* at nerve- and neurosecretory cell-endings ("neurohormones" of Welsh, 1955).
        - (iv) Diffusion unrestricted, the substances passing out of the tissues and into the surrounding medium to act on other individuals, usually of opposite sex. These include "*gamones*" and "*ectohormones*".
    - (b) *Circulatory activators* or *vascular hormones*, distributed to all parts of the body in the blood circulation, so that their actions must be limited by the sensitivity or competence of the tissues which they reach. They may be secreted by:
        - (i) *Isolated cells* such as those of unknown origin in the gut mucosa of vertebrates (§ 2.21).

(ii) *Neurosecretory cells* with the swollen ends of their original axons forming storage-and-release organs ("neurohaemal organs" of Knowles and Carlisle, 1956), that make contact with blood vessels (§ 2.11).

(iii) *Endocrine gland cells*, which secrete internally into the blood and are formed from almost any tissue of the body, including the nervous system (in which case the distinction from neurosecretory cells is only one of the degree of their histological modification).

The chemical activators to be considered as "animal hormones" in the present book are the circulatory activators, or vascular hormones (2 b). Yet since there is really no logical point at which some of them can be separated from other neurosecretions, or even from the organisines which have actions so much like those of morphogenetic hormones, reference to these will have to be made in the relevant sections, as will chemicals involved in nervous stimulation, where their functions overlap those of hormones.

The complex interaction of many of these chemical activators is well illustrated by considering the way in which genes initiate, and hormones complete, the differentiation of the gonad rudiment into a testis or an ovary within an embryo, the development of which starts under the general control of an organizer, continues by progressive chemodifferentiation, and cannot be completed without the combined action of the nervous system and yet other hormones!

1.3 MECHANICAL ACTIVATION

The only other means made use of by animals for co-ordinating their activities is purely mechanical. This can act in the absence of nerves or of any chemical activators, and may well be a primitive way of transmitting control. The action of a current of water stimulating the sponge osculum to remain open appears to be purely mechanical, but it is not certain that some chemical may not be diffusing from cell to cell. The best example is in the locomotion of the earthworm, where the muscles contracting in one segment stretch those in the adjacent segment behind, and stimulate them to contract in their turn to give a wave of contraction passing back from segment to segment. This is a primitive method of control which may be supposed to have preceded that by the nervous system.

A distinct contrast to this is afforded by the use of mechanical distention of the stomach as a means of initiating the secretion of GASTRIN, one of the hormones from the mammalian gut. For in this case mechanical stimulation, like the direct chemical stimulation which acts upon other endocrine cells in the same region, seems to be part of a highly specialized system for harmonizing the successive stages of digestion, and to have succeeded the nervous control that is used for a similar purpose by cold-blooded vertebrates (§ 4.11).

1.4 Definitions of hormones

The simplest and earliest definition of hormones as "chemical messengers" must be amplified, if it is to limit the use of the term "animal hormones" to the circulatory activators.

A well-established definition of a hormone is "a physiologic organic compound produced by certain cells and carried by the blood to distant cells, the activities of which it influences" (Selye, 1947). This is still rather too loose a definition; it accords more nearly with what has been termed a "humoral mechanism", or "a process which has been demonstrated to be independent of nervous connections between the site of stimulation and the effector site, and is, therefore, considered to be transmitted by a blood-borne substance, but in which the hormonal or non-hormonal nature of the blood-borne substance may be uncertain" (Grossman, 1950). This refers particularly to substances like histamine, which may occur in the blood in the abnormal conditions of an experiment and yet play no part in normal physiology, and to the so-called "secretagogues". These last are substances that may be found in extracts of gut cells; they have the capacity to stimulate enzyme secretion by the gut glands but are not natural secretions (§ 4.11).

It has already been indicated that a hormone is not necessarily secreted by a gland, nor is its secretion by any means always stimulated by nerves, as some elementary definitions have suggested (e.g. Yapp, 1942). A sound definition must be such as to include GASTRIN, which comes from isolated cells and for which the stimulus to secretion is the direct action of mechanical pressure in the gut lumen, and also INSULIN, which comes from small groups of gland cells and for which the stimulus to secrete is the level of glucose concentration in the blood. It must also include the hormones which stimulate the secretion of other hormones, like the INTERSTITIAL-CELL-STIMULATING HORMONE from the adenohypophysis, which stimulates the secretion of TESTOSTERONE from the testis, as well as those hormones the action of which is inhibitory rather than activating.

Huxley (1935) suggests that a hormone is "a chemical substance produced by one tissue, with the primary function of exerting a specific effect of functional value on another tissue"; but, as he admits, this has the teleological implications of any functional account. Moreover, it loses sight of the fact that some chemical substances, such as adrenaline, are present as by-products with no apparent function in many primitive animals, and seem only to have been salvaged for use as hormones in the more highly evolved phyla.

It is also well to remember that hormones, or their active constituents, are usually rather stable compounds, able to persist for some time in the blood stream and yet composed of molecules sufficiently small to pass through the walls of blood capillaries and cell membranes to reach their targets.

The *vascular hormones*, with which this book is mainly concerned, may best be defined as *specific organic substances produced by isolated cells, or by a tissue which may form a gland; they activate or inhibit effects of functional value occurring in other cells or tissues, to which they are carried in the blood.*

1.5 TYPES OF HORMONES

Although many actions in a wide range of animals can now be attributed to hormones, it cannot be expected that any functions will belong to hormones alone; rather must they be recognized as playing but a small part within the complex co-ordination of metabolic and other processes that supply and direct the food and energy as between the multifarious daily activities of the animal and its growth and reproduction. These processes must be controlled to fit the frequent changes both within the animal and in its environment. At different times of the day, or the tide, or the year, the energy must be directed to different purposes, to serve the needs of both individual and race survival. The greater part of this control is achieved by the nervous system; but hormones may come in at almost any point, sometimes independently, but more often in direct or indirect response to nerve stimulation.

It is not merely convenient to review the hormones in relation to their actions; it also allows of some interesting comparisons being made between those having similar actions in invertebrates and vertebrates, and reveals a notable degree of correlation between some of their actions and the sources from which the hormones come. It also shows certain striking gaps: some animals lack hormones with particular actions; many invertebrate phyla, or classes, lack hormones altogether. It may be supposed that in many cases the main detectable actions of a hormone represent its physiological functions within the normal animal; but other actions, which are apparent experimentally, may be accidental and without true functional significance. Their actions will be considered under three main headings:

(1) *Kinetic*, or the control of effectors (§ 1.51 and §§ 3 and 4);
(2) *Metabolic*, or the control of cell biochemistry (§§ 1.52 and 5);
(3) *Morphogenetic*, or the control of growth and differentiation (§ 1.53, and Part II, to be published separately).

Each of these groups can be further subdivided in relation to the particular organs or processes controlled (Table 1). This grouping of hormones is not yet widely used; but it has been found in practice to afford a very good working framework within which to consider the available information, with the minimum of ambiguity or overlap. It has been accepted in a recent presentation of crustacean hormones (Carlisle and Knowles, 1959), together with the terms kinetic and endocrinokinetic suggested to them by the writer (Carlisle and Jenkin, 1959). The term kinetic hormone corresponds to their previous term of "energetic hormone" (Knowles and Carlisle, 1956).

TABLE. 1. SUMMARY OF THE MAIN TYPES OF ACTION OF VASCULAR HORMONES

	ACTION	EXAMPLES *	
		VERTEBRATE	INVERTEBRATE
PART I	KINETIC		
§ 3.1	Contraction of muscle	Adrenaline	Corpus cardiacum
3.2	Concentration and dispersion of pigment	W and B†	PLH and PDH
4.1	Secretion of exocrine glands	Secretin	Gonad
4.2	Secretion of endocrine glands	ACTH	Intercerebral neurosecretory cells
PART I	METABOLIC		
§ 5.1	Control of respiration rate	Thyroxine	Corpus allatum
5.2	Carbohydrate and protein balance	Insulin	Sinus gland
5.3	Eloctrolyte and water balance	ADH	Brain
5.4	Ca and P balance	Parathormone	Y-organ
PART II	MORPHOGENETIC		
§ 3	General growth	"Growth", STH	Sinus gland ?
	Moulting	Thyroxine	Y-organ
	Metamorphosis	Thyroxine	Prothoracic gland
	Regeneration	STH	"Organisine"
	Growth of glands	Thyroxine ?	(source unknown)
§ 4	Gonad maturation	FSH	Corpus allatum
	Gamete release	LH	Corpus allatum
	Differentiation of genital ducts	Oestrone or Testosterone	Testis
	Development of secondary sexual organs	Testosterone	Vas deferens gland

* See tables in each section for complete lists of the hormones and their sources referred to in this book.

† See glossary.

1.51 KINETIC HORMONES

The kinetic hormones act upon effector cells or organs, to produce repeatable reactions mainly concerned with feeding, digestion and protective colour change, and so are often related to the short-term interaction of the individual with its environment. The results that they produce are relatively rapid compared with other types of hormone action, but considerably slower and more long-lasting than the nerve action which often controls similar effectors. Their action is also more widespread than that of nerves, since they are distributed by the circulation throughout the body, and cannot, as a rule, be used to cause the contraction of one muscle and not another, or to produce a pattern by concentrating some chromatophores and dispersing others, unless the effectors themselves are differentiated.

Many, but by no means all, of the hormones in this group are neurosecretory substances (2b. ii, p. 4). Most of the others come from ectodermal glands (2b. iii), except the notable group produced from the isolated cells (2b. i) in the mammalian gut. The last-named are stimulated directly (§ 4.11); but the rest are all controlled by the nervous system, apart from a few anomalous hormones which appear to have kinetic actions but to be derived from mesodermal glands (§ 4.324).

There is one group of hormones within the kinetic type which calls for special mention at this stage, and for an elucidation of the rather confused nomenclature associated with it. These are the hormones for which the name *endocrinokinetic* is adopted here. They all stimulate the secretion of other hormones from endocrine glands (2b. iii), and it seems logical to class this action, with that of stimulating exocrine glands, as kinetic. But the situation in which a series of two hormones is involved is more complex than those with but one hormone, and it seems to warrant somewhat different treatment. These endocrinokinetic hormones are frequently designated by the suffix "trophic" or "tropic", as in thyrotrophic or gonadotropic; but the suffix is not confined to this type of hormone, since it also occurs in chromatophorotrophic, where the effector is a chromatophore, and not an endocrine gland at all. Even the international decision taken in 1939 that the form trophic should be used in all cases has led to no uniformity of spelling!

Among vertebrates all the endocrinokinetic hormones are secreted by the adenohypophysis (anterior lobe of the pituitary body); but so also are hormones with such morphogenetic actions as stimulating the growth and maturation of the gonads. Yet the term trophic or tropic has been applied indiscriminately to both, as in the case of the gonadotrophins, of which the interstitial-cell-stimulating hormone, ICSH, is endocrinokinetic and causes hormone secretion from the gonads, but the follicle-stimulating hormone, FSH, is morphogenetic and causes their growth. There are as yet no separate names for the similarly separable actions of the thyrotrophic hormone, TSH, or of the adrenocorticotrophic hormone, ACTH; but there is a mounting body of evidence to show that the two types of action are often, and perhaps always, due to distinct, albeit closely similar hormones (§ 4.2). If in some cases the two actions are really inseparable, they may perhaps be likened to the motor and trophic actions of one and the same nerve.

There are still a few effectors for which no example of kinetic hormone control is known: namely, luminous and electric organs among those usually controlled by nerves, and flagella and nematocysts among those for which no internal control is known.

1.52 METABOLIC HORMONES

The metabolic hormones are concerned particularly with the control of metabolic activities, at the physico-chemical or biochemical level, within the cells of the animal, e.g. with adjustment of respiratory rate (§ 5.1), supply of sugars and proteins to the tissues (§ 5.2), and their electrolyte and water balance (§§ 5.3 and 5.4). Such processes often have a basic rate that seems to be an intrinsic or genetic property of the cells which carry them out. The rates are rarely under nerve control, but hormones may induce changes in them; in many instances, a pair of hormones act together, one increasing the rate and the other decreasing or inhibiting it. This is particularly clear in the control of electrolytes and water in the vertebrate kidney (§ 5.3). Many of the metabolic hormones in Arthropoda are products of neurosecretion, and stimulate the rate of the process in question but are themselves subject to nervous inhibition. Other metabolic hormones, especially in vertebrates, are secreted by endocrine glands and are subject to control by endocrinokinetic hormones. The nervous system takes but a small share in their control, except in emergencies such as haemorrhage or other forms of shock. More often the equilibrium is maintained by a "feed-back" system, whereby the accumulation of some product of the hormone's action inhibits further secretion of the hormone until the accumulation is again reduced. This applies directly to some metabolic hormones, and indirectly to others, through its control of the endocrinokinetic hormones that stimulate them (§ 5.5).

1.53 MORPHOGENETIC HORMONES

The morphogenetic hormones produce long-term changes that involve cell division, growth and differentiation; in contrast to the quick-acting kinetic hormones, their effects can neither be reversed nor repeated, at least for a considerable time. Formerly, these hormones were grouped under a more widely defined "metabolic" heading. There was some justification for this, in that growth is not possible without an adjustment of the metabolic processes to provide the growing cells with the necessary building materials for protein synthesis, and energy supplies in the form of glucose (cf. §§ 5.2 and 5.5). Yet these and other metabolic processes continue throughout the life of the animal, and are not necessarily linked to morphogenesis, which is often intermittent, as is easily seen in moulting and metamorphosis and in the changes associated with seasonal reproduction.

Morphogenetic hormones affecting growth and regeneration are present in several phyla, including Annelida and Mollusca, from which no metabolic hormones have so far been reported, and the means of controlling them is, in many cases, still unknown. It is only in Crustacea, Insecta and Vertebrata that nearly all the morphogenetic factors are secreted as vascular hormones and are controlled by endocrinokinetic hormones, which link the processes of growth, differentiation and reproduction indirectly to the nervous system, and thence to seasonal changes in the environment (§ 4.232).

Hormonal control of moulting and metamorphosis is now well known in Crustacea and Insecta, in both of which ectodermal glands from the antennary or maxillary segments secrete moult-promoting hormones. Their secretion is stimulated by an endocrinokinetic hormone, prothoracotrophin, in Insecta (§ 4.211), and probably by a similar hormone in Crustacea. Otherwise the two classes differ in that, in the latter, moulting is restrained by a moult-inhibiting hormone; this does not occur in Insecta, in which a so-called juvenile hormone from the corpora allata inhibits metamorphosis only. The initiation of metamorphosis in Amphibia by thyroxine, with its dependence on the availability of iodine, was an early discovery; its control by the endocrinokinetic thyrotrophin, TSH, was established later.

The differentiation of the genital ducts and other sexual characters has also been found to depend on hormones in a number of invertebrates, as well as in vertebrates, where the pattern of control differs in detail in different classes (§ 4.234 and Part II, § 4). Only a few of the hormones producing these effects are shown in Table 1; their detailed treatment is reserved for the second Part of this work.

The so-called "organisines", which stimulate regeneration in Platyhelminthes, are not vascular hormones, since in the absence of any circulation in these animals it must be assumed that the substances diffuse through the tissues in a way that is reminiscent of embryonic organizers, as their name suggests (Dubois and Lender, 1956).

1.6 Identification

The technique of finding, testing and confirming the presence and action of a hormone is exacting, and needs many controls if the results are to be conclusive. It is difficult if only a single hormone with a relatively clear-cut effect is under investigation; for quite a long series of experiments is needed to elucidate the situation. All too often some steps in the proof are missing, either for technical reasons or because their importance was not fully realized during the early stages of hormone investigation.

Histological examination of tissues that are suspected of secreting hormones is one side of the investigation, since cells capable of this type of chemical activity often have a recognizable cytological appearance (Figs. 2-2 and 4-7), with granular precursors of the secretion and enlarged nuclei. Once the secreting cells have been located, it may be possible to make extracts of tissue containing them, and to compare this with extracts of adjoining tissue containing no such cells, in order to arrive at more definite results than can be obtained from extracts of whole structures like the crustacean eyestalk (§§ 3.12 and 3.223).

A carefully planned experimental investigation is also essential if the action of the hormone is to be fully established. This usually falls into one of two categories, the pharmacological or the physiological: in the first, it is shown that certain extracts, or chemicals, have effects upon the animal, such as stimulating muscle contraction, or raising the salt output in the urine; in the second, and usually more difficult category, an attempt is made to prove that the chemical in question is used in the normal physiology of the animal to control the same process.

In general, it can be said that if only one hormone is concerned, its control of a certain reaction can be sufficiently proved if adequately controlled experiments show that:

(i) removal of the source of the hormone is followed by loss of the reaction,
(ii) injection of an extract from the source can restore the reaction,
(iii) removal of any other structure does not cause loss of the reaction,
(iv) injection of any other extract does not restore the reaction.

It is better if the reaction is shown by an organ with no nerve connections, and if it can be interrupted by ligation of its blood supply. If the reaction can be restored by injection or transfusion of blood from another individual in which hormone secretion has been stimulated by natural means (cf. Fig. 3-3), the proof that this hormone plays a part in the natural physiology of the animal is more convincing. To complete the identification of any particular hormone, it may be necessary to separate it from others which can be extracted from the same source, and the problem is never finally elucidated until the chemical constitution of the pure hormone is known.

If more than one hormone is involved in the control of a reaction,

TABLE 2. STEPS IN ESTABLISHING DIRECT AND INDIRECT ACTIONS OF TWO INTERACTING HORMONES

EXPERIMENTS ON RATS	RESULT	CONTROLS ON LITTER MATES PREFERABLY OF SAME SEX	RESULT
1. Operative removal of the adrenal cortex	Death	1*a*. Mock operation	Survival
2. Op: as 1 + injections of pure cortex extract	Survival*	2*a*. Op: as 1 + other injections†	Death
3. Op: removal of Adhp: (including source of ACTH) leaving cortex intact but unstimulated	Death	3*a*. Mock operation	Survival
4. Op: as 3 + injection of one fraction of Adhp: extract (=ACTH)	Survival*	4*a*. Op: 3 + injections of any other Adhp: extracts	Death
5. Op: removal of Adhp: and cortex	Death	5*a*. Mock operations of equal severity	Survival
6. Op: as 5 + injections of ACTH (as 4)	Death	6*a*. Op: as 5 + injection of other extracts	Death
7. Op: as 5 + cortex extract (as 2)	Survival*	7*a*. Op: as 5 + injection of other extracts	Death

* For as long as injections are maintained.

† NaCl injection can mitigate the effect of cortex removal for some time (§ 5.311).

Adhp = adenohypophysis. ACTH = adrenocorticotrophin.

Argument: Experiments 1 to 4. The result of removing either the cortex or the adenohypophysis is the same (1 and 3). So is the effect of injecting extracts of the gland removed, i.e. replacement of either missing hormone can maintain life (2 and 4). The operation itself and post-operative shock as causes of death are ruled out by survival of controls (1*a* and 3*a*), on which operations of comparable severity are performed, but without touching the endocrine organs. Injections of other materials are shown by controls to be ineffective (2*a* and 4*a*). By fractionation of the extracts of the adenohypophysis, and by testing each separately (4), it is shown that ACTH is the only effective substance.

At this point it still remains an open question as to whether the two hormones that have been identified have independent actions, or whether one is direct and the other indirect, as it would be if one were an endocrinokinetic hormone.

Experiments 5 to 7. The results of these further experiments and their controls give the minimum of information upon which these questions can be decided. CORTEX EXTRACT alone is effective in the absence of both sources (7), and is therefore the direct metabolic hormone, whereas ACTH is ineffective (6), unless the CORTEX TISSUE is present (4). Since the unstimulated cortex is ineffective (3), the action of ACTH must be to stimulate the cortex to secrete (as in the normal animal, and in experiments 1*a* and 4).

Conclusion: ACTH is, therefore, the *endocrinokinetic hormone* stimulating the secretion of a *metabolic hormone* from the adrenal cortex.

the experimental investigation becomes more complex. The tabulated theoretical scheme for a set of experiments, to show the relation of a metabolic hormone from the adrenal cortex and the adrenocorticotrophic hormone, ACTH, from the adenohypophysis (Adhp. Table 2), is given as an indication of the minimum number of experiments involved.

Taking "death" or "survival" of the animal as the criterion of the hormone's action is obviously much too crude, and should be replaced by some surer physiological test of the metabolic activities affected, such as the measurement of blood-sugar; but in that case, the opposing action of insulin has also to be taken into account (§§ 4.2 and 5.2).

For obvious reasons of space it will not be possible in the cases cited below to give full details and results of all the experiments upon which the conclusions are based; but an attempt will be made to give some of the clearer examples in enough detail to indicate how far the technique of the original work was satisfactorily controlled.

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CHAPTER 2

SOURCES OF KINETIC AND METABOLIC HORMONES

Before describing the actions of the various kinetic and metabolic hormones, an account will be given for reference of the sources from which they are derived and of some of the ways in which they reach the blood stream.

The cells in the animal body which are able to secrete hormones into the blood can be conveniently grouped by their embryological origins. Invertebrate examples will be given first. It will then be noted that the sources of those kinetic and metabolic hormones that are so far known from invertebrates all come from the ectoderm (§ 2.1) and that it is only in the vertebrates that the endoderm (§ 2.2) and the mesoderm (§ 2.3) also provide sources for these kinds of hormones. The sources of morphogenetic hormones, which affect growth, differentiation and reproduction, include the gonads of both invertebrates and vertebrates, as well as the ectodermal glands which secrete moulting hormones in the Arthropoda, namely, the Y-organ in Crustacea and the prothoracic glands and their homologues in Insecta. Passing references will be made to some of these morphogenetic hormones in the chapters that follow, but their main actions and details of their sources will be described in Part II.

2.1 Ectodermal sources

The hormone-secreting, or endocrine, cells which are formed from the embryonic ectoderm can be divided into those which arise from the nervous system (§ 2.11) and those which arise from non-nervous epithelium (§ 2.12); but the distinction may be rather arbitrary, since the stomodaeal epithelium of the cephalopods gives rise to non-nervous cells, whereas that of insects gives nervous cells.

2.11 SECRETORY CELLS DERIVED FROM THE NERVOUS SYSTEM

A large number of hormones in many phyla are now known to be secreted by nerve cells or their derivatives (Fig. 2-1). Some of these have become so specialized for secretion that they have lost almost all histological semblance of neurons, and their connection with them is only apparent in their development or in the quality of their secretion. Of such are the cells of the corpus cardiacum of insects and the adrenal medulla of vertebrates (Fig. 2-1*e* and *f*). On the other hand, many secretory cells derived from neurons come within the histological definition of NEUROSECRETORY CELLS; these have only recently been recognized as sources of hormones because they are less easy to discern than the compactly aggregated endocrine glands, formed by most other cells of internal secretion. They differ from neurons in secreting microscopically visible quantities of granules or droplets, while retaining such characters as Nissl bodies in the cytoplasm and axons with neurofibrillae; they may or may not have dendrites (Fig. 2-1*b*, *c* and *d*). There seems to be no real need to separate neurosecretory cells, which secrete hormones into the blood, from any other endocrine cells derived from either the nervous system or any other part of the ectoderm, for their secretory activity is similar, although their histological form is different. Since, however, much attention has been focused recently upon neurosecretion, it will be well to summarize some of the main points about it.

Neurosecretory cells have been identified in animals representing most of the phyla with centralized nervous systems; but as yet their production of vascular hormones has only been demonstrated in a relatively small proportion of these phyla. In some of these phyla, and notably in Annelida, they are only known to yield morphogenetic hormones (Part II); but in the Mollusca, Arthropoda and Vertebrata neurosecretory cells are known to secrete vascular hormones with kinetic and metabolic actions.

Neurosecretory cells can usually be recognized within the nervous system by their large size (often 30 μ or more in diameter), with large nuclei and secretory granules in the cytoplasm; but the latter may vary with the phase of the secretory cycle. This will affect both the microscopic appearance of the cells (Fig. 2-2) and their reaction to histochemical tests which can be applied to the secretion. Some of these cells appear to release their secretion, or neurohormone, where it can only diffuse through the closely adjacent tissue without reaching the circulation. It is then difficult to distinguish the action experimentally from that of a normal motor nerve, especially as the release of secretion is probably accompanied by electrical changes in the axon similar to those accompanying the nerve impulse. The distinction between such cells and ordinary neurons seems only to be one of degree, for it depends upon the presence or absence of "granules". This in turn depends rather arbitrarily upon the limits of resolution of the ordinary light microscope. Since the abundant fine granules of adrenaline, which stain brown with chromates, can be readily seen with the light microscope in cells of the adrenal medulla, there seems little reason to doubt that the minute quantities of the same substance, secreted at sympathetic nerve endings, could also be seen by using the greater magnification that can now be achieved by the electron microscope. Yet these nerves are not usually considered to be neurosecretory. Other neurosecretory cells have simple axon endings that discharge their secretion into blood vessels, thereby clearly acting as a source of a vascular hormone.

The secretion is formed as granules or droplets either in the cytoplasm immediately surrounding the nucleus, or within the nucleus itself. Thence the granules have been seen to move slowly along the axon and are probably carried in the axoplasm current, which flows at a rate of about 3 mm per day (the movement of endoneural fluid is about 20 times as fast). They accumulate at the unbranched ends of the axons, which become swollen and are often aggregated together to form a storage-and-release organ at the point where the hormone is passed into the blood. Such structures have been called neurohaemal organs (Carlisle and Knowles, 1953). The secretion can sometimes be detected for a short distance even after its discharge into the blood vessel.

It is probable, however, that the visible secretion often acts as a "carrier", to which is attached the chemical substance that acts as the hormone. The carrier may be some large molecule, like a protein, which helps to anchor the smaller hormone molecule in the cell until the time for its release. The hormone is then separated from the carrier, and apparently becomes free to enter the blood and be passed on to the tissues. The carrier is usually visible in the living cells by dark-ground illumination because of its highly refractile granules which show up as bright spots (Fig. 2-3); in fixed preparations the carrier often stains, in a characteristic but not specific way, with Gomori's chrome haematoxylin phloxin and other stains, such as Mallory's triple stain for connective tissue (Scharrer and Scharrer, 1954*a*).

There is increasing evidence that neurosecretory cells not only secrete a greater quantity of some active chemical substance than do typical nerve cells, but that they may also be specialized to produce a greater variety of substances than just the acetylcholine or adrenaline and noradrenaline of nerve endings. Recently, five distinct staining reactions have been found among the neurosecretory cells terminating in the sinus gland of a crab (§ 2.112; Potter, 1954), and it seems likely that eventually these will be found to be related to separate hormones.

The occurrence of neurosecretory cells, which release hormones that have either kinetic or metabolic actions, is given with the other sources in Table 3. The last column shows the later sections of the book in which examples of these actions are described. A more detailed summary of the occurrence of neurosecretion in invertebrates can be found elsewhere (Gabe, 1954).

2.111 *Epistellar body of Cephalopoda*

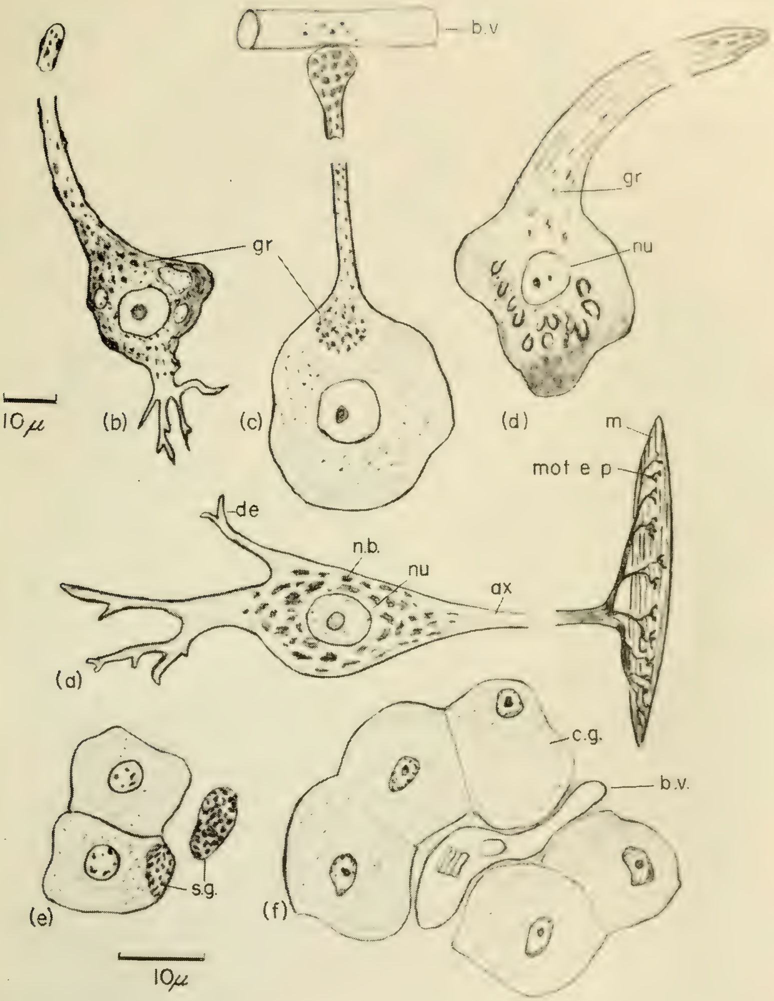
In most octopods there is a small compact body on the outer surface of the stellate ganglion in the mantle cavity. In *Eledone moschata* it is yellow and about the size of a pin's head. Microscopic examination shows this epistellar body to contain a group of neurosecretory cells (Fig. 2-1*d*) with their axons converging on a central cavity, which contains secreted granules in a homogeneous ground substance. The granules presumably release a hormone into the adjacent artery; but its ability to stimulate muscle tone in the mantle (§ 3.12) has only been postulated from extirpation experiments.

TABLE 3. ECTODERMAL SOURCES OF KINETIC AND METABOLIC HORMONES

SOURCE OF HORMONE	STORE OF HORMONE (OR NAME)	TYPE OF ACTION*	SECTION NO.
2.11 CELLS FROM THE NERVOUS SYSTEM			
2.111 *Epistellar body of Cephalopoda*			
Stellate ganglion	Epistellar body	K	3.12
2.112 *Neurosecretory systems of Crustacea*			
Ganglionic-X-organ and brain	Sinus gland	K	3.222
,, ,,	,, ,,	K	3.223
,, ,,	,, ,,	M	5.112
,, ,,	,, ,,	M	5.122
,, ,,	,, ,,	M	5.211
,, ,,	,, ,,	M	5.321
,, ,,	,, ,,	M	5.422
,, ,,	Hanström's sensory pore organ	EK	4.211
Commissures	?	K	3.223
Pericardial organs	?	K	3.111
Eyestalk tip	?	M	5.223
2.113 *Neurosecretory systems and glands of Insecta*			
Protocerebrum	Corpora cardiaca	EK	4.211
,, ,,	?	M	5.321
Suboesophageal ganglion	—	K	3.221
,, ,,	—	M	5.112
Corpora cardiaca	—	K	3.111
2.114 *Neurosecretory systems and glands of Vertebrata*			
Paraventricular and supra-optic nuclei of hypothalamus	Neurohypophysis	K	3.114
	,, ,,	M	5.312
,, ,,	,, ,,	M	5.322
Supra-renal tissue	(Adrenaline)	K	3.112
Adrenal medulla	(Adrenaline)	K	3.112
,, ,,	,,	K	3.116
2.12 GLANDS FROM ECTODERMAL EPITHELIUM			
2.121 *Salivary glands of Cephalopoda*			
Salivary glands	(Tyramine)	K	3.21
2.122 *Corpora allata of Insecta*			
Corpora allata	—	M	5.111
2.123 *Adenohypophysis of Vertebrata*			
Pars distalis	(TSH)†	EK	4.221
,, ,,	(STH)	EK	4.223
,, ,,	(ACTH)	EK	4.231
,, ,,	(ICSH)	EK	4.232
,, ,,	(LSH)	EK	4.232
Pars intermedia	(B or MSH)	K	3.223
Pars tuberalis	(W)	K	3.223

* K = kinetic. EK = endocrinokinetic. M = metabolic.

† See glossary.



b.v
gr
gr
nu
10μ
(b)
(c)
(d)
m
mot e p
de
n.b.
nu
ax
(a)
c.g.
b.v.
s.g.
(e)
(f)
10μ

FIG. 2-1 (*a–f*)
(*For legend see over*)

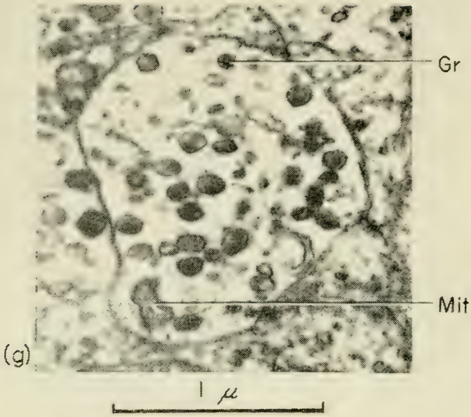


FIG. 2-1 (*g*)

FIG. 2-1. Cells derived from the nervous system. (*a*) Typical motor *nerve cell* with branched dendrites (de), cell body with Nissl bodies (n.b.) in cytoplasm, nucleus (nu) with nucleolus, and long axon (ax) branching to motor end-plates (mot.e.p.) on muscle fibres (m). (*b—d*) *Neurosecretory cells* with stainable granules (gr): (*b*) with dendrites, from supraoptic nucleus of dog (after Scharrer and Scharrer, 1954*b*); (*c*) without dendrites, the blunt axon is swollen with secretory granules that pass to a blood vessel (b.v.) from ganglionic-X-organ of crab, *Sesarma* (after Enami, 1951). (*d*) cell with shorter axon, from epistellar body of *Eledone* (after Young, 1936). All drawn roughly to upper scale. (*e*) and (*f*) *Gland cells* with secretory granules (s.g.) but no histological characters of neurons (drawn to lower scale): (*e*) cells from corpus cardiacum of beetle, *Hydrous* (cf. Fig. 2-9 after de Lerma, 1956); (*f*) cells round blood space (b.v.) from adrenal medulla of a tetrapod, with "chromaffin" granules (c.g.) (after Maximow and Bloom, 1942). The differences in quantity of secretion are not characteristic of these cells, but indicate different phases of secretion (cf. Fig. 2-2). (*g*) Electron micrograph of a highly enlarged section across the axon of a neurosecretory cell from the neurohypophysis of a cat, showing fine granules (Gr) 0.1 to 0.3 µ in diameter, and mitochondria (Mit) that are larger (from Bargmann, 1958).

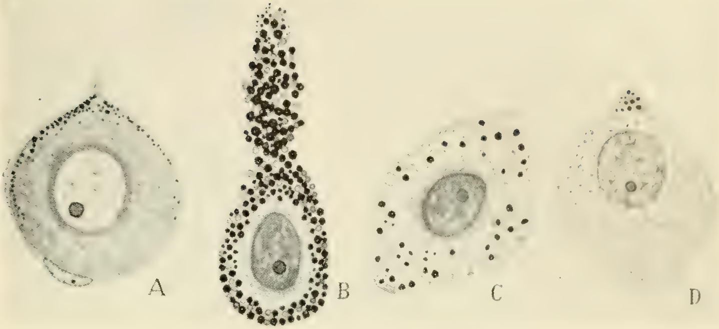


FIG. 2-2. Neurosecretory cells, with axons cut short, from the suboesophageal ganglion of the cockroach, *Leucophaea maderae*. The differences probably correspond to phases in a secretory cycle: (A) laying down fine granules in the cell-periphery in the position of Nissl bodies at the onset of secretion; (B) abundant larger granules passing into the swollen axon above; (C) empty vacuoles replacing secretory droplets; (D) an almost empty cell body, with only a few granules left at the base of the axon. The cycle then probably starts again at (A); but the sequence has not yet been proved. Cells, × 320, fixed in Zenker-formol and stained in Masson (from Scharrer and Scharrer, 1954*b*).

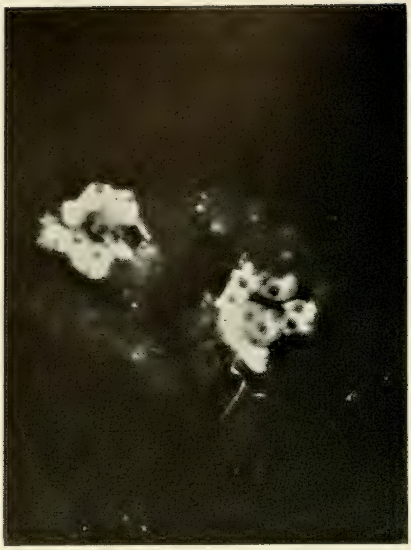


FIG. 2-3. Living median neurosecretory cells in the protocerebrum of the blowfly, *Calliphora*, photographed by dark-ground illumination. The secretory granules in the cells are highly refractile and therefore show as bright areas filling the cell bodies; only the nuclei remain dark. Other brain cells without granules can be seen faintly outlined in the background (from E. Thomsen, 1954).

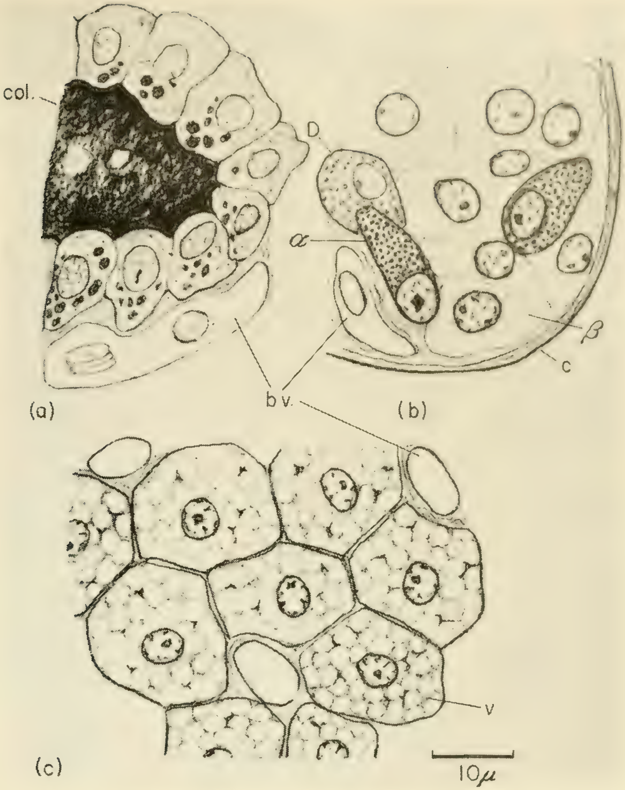


FIG. 2-14. Endocrine cells from the endoderm and the mesoderm of mammals. (*a*) Follicle of the THYROID gland, enclosing colloidal store (col.) of secreted diiodotyrosine; this precursor substance is later reabsorbed by the cells, converted to thyroxine and passed to the blood vessel (b.v.) through the outer cell surface (cf. Figs. 4-7 and 4-8). (*b*) Three kinds of cells in an islet of Langerhans stained with Mallory-azan: α cells that secrete GLUCAGON and have coarse granules that stain red; pale β cells that secrete INSULIN and have fine granules that stain red; D cells that have no known function and stain blue; b.v., blood vessel, c., capsule of connective tissue. (*c*) Mesodermal cells, forming part of ADRENAL CORTEX; they are shown in close contact with each other, and with capillaries of the blood supply (cf. Fig. 2-15). The vacuolated cytoplasm (v.c.) is shown after removal of all fat, which is abundant in living cortical cells (after Maximow and Bloom, 1942 and Pauly, 1957).

The epistellar body is of interest, not only because the term neurosecretory was first used in this country to describe its cells, but also because it provided some of the earliest evidence for the conversion of neurons into secreting cells in an invertebrate (Young, 1936). The corresponding nerve cells in the stellate ganglia of decapod cephalopods still retain the form of neurons, but have their axons fused to form giant fibres to the mantle muscles. They are scattered in *Sepia*, but collected together in the same position as the epistellar body in *Loligo* (Fig. 2-4). These neurons, as well as the neurosecretory cells of the epistellar body, are innervated by axons coming from the pedal ganglion of the brain.

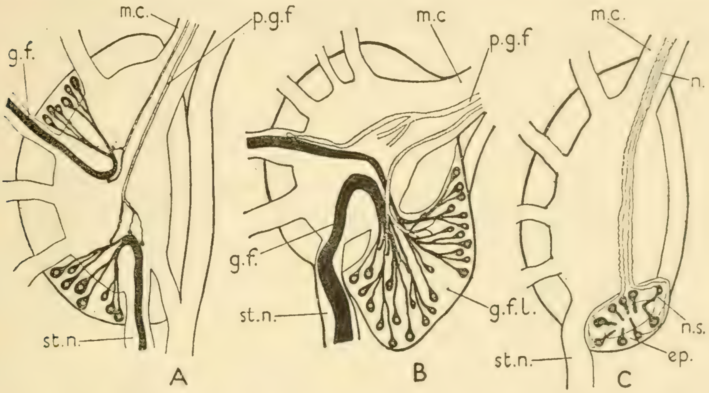


FIG. 2-4. The stellate ganglia of *Sepia* (A) and *Loligo* (B), and the epistellar body of *Eledone* (C). In (A) the giant fibres (g.f.) and the stellate nerve (st.n.) arise from nerve cells that are scattered throughout the ganglion; in (B) they are collected into a lobe (g.f.l.). In the octopus (C) there are no giant fibres, but instead there are neurosecretory cells (n.s.) whose axons end blindly in the central space of the epistellar body (ep.); their secretion passes in the blood to the mantle muscles. A nerve (n.) to the epistellar body replaces the preganglionic fibres (p.g.f.) to the nerves in (A) and (B), and presumably controls the release of secretion in (C). (From Young, 1936).

2.112 *Neurosecretory systems of Crustacea*

There are four neurosecretory systems in crustaceans. Two of these have their nucleated cell bodies in the brain and in the optic

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lobes; the ends of their secreting axons are aggregated into distinct storage-and-release organs, known as the sinus gland and Hanström's sensory pore organ respectively.

A third group of neurosecretory cell bodies has been found in

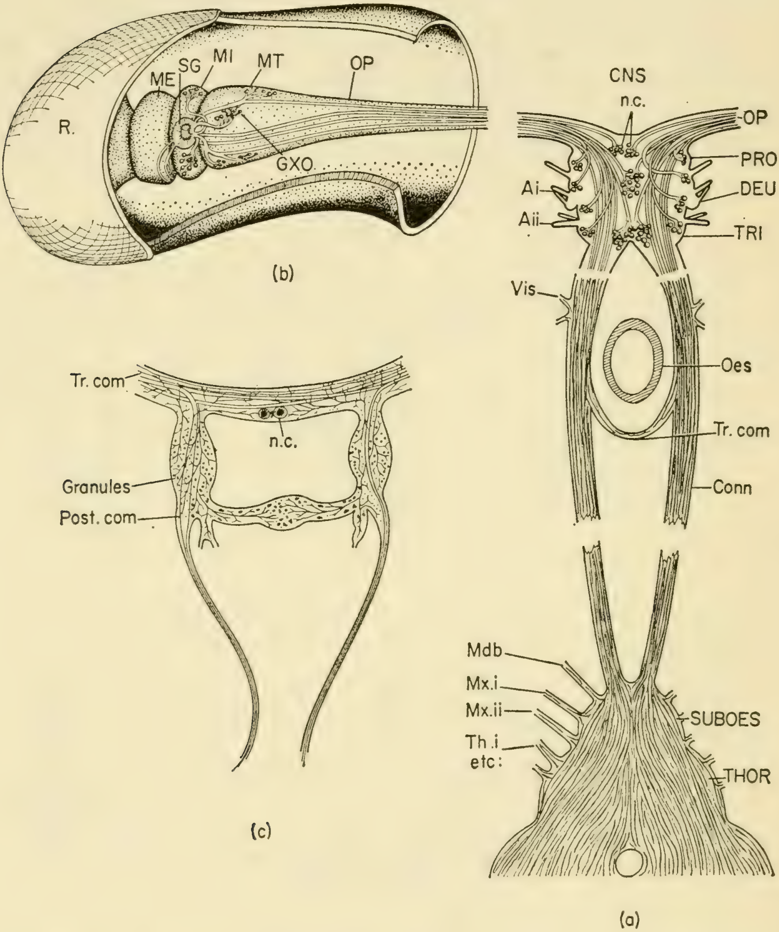
R.
ME
SG
MI
MT
OP
GXO
(b)
CNS
n.c.
OP
PRO
DEU
Ai
Aii
TRI
Vis
Oes
Tr. com
Conn
Tr. com
n.c.
Granules
Post. com
(c)
Mdb
Mx.i
Mx.ii
Th.i
etc:
SUBOES
THOR
(a)

Fig. 2-5. Neurosecretory cells (n.c.) in decapod Crustacea. (*a*) Brain, connectives and fused ventral ganglia of a crab, *Gecarcinus*, and (*b*) eyestalk of *Gecarcinus*, cut open dorsally to expose the

the commissures and connectives arising from the brain, and extracts showing hormonal activity have been obtained from them (§ 3.223); but the natural point of release for their secretions into the blood stream is uncertain. It may be the post-commissure organs (Knowles, 1953).

A fourth system has been found in the pericardial organs of various decapod crabs and of Stomatopoda; these also yield an active extract (§ 3.11), but a natural secretion has not been fully established.

Brain, ganglionic-X-organ and sinus gland

Some of the neurosecretory cells, that release their secretion in the SINUS GLAND, have their cell bodies in the PROTOCEREBRUM of the brain and others in its extension into the TERMINAL MEDULLA of the optic lobe. The details vary for different orders and species. For instance, in the crab, *Gecarcinus*, the cells extend from the protocerebrum into the deutero- and tritocerebral lobes of the brain (Fig. 2-5*a-b*; Bliss and Welsh, 1952).

The relatively large group of neurosecretory cells (Fig. 2-7) that lies in the terminal medulla is best known as the GANGLIONIC-X-ORGAN (pars ganglionaris X organi of Carlisle, 1953).

It is important to remember the positions of these neurosecretory cells in experimental work. Removal of the whole eyestalk removes the ganglionic-X-organ but leaves the cell bodies

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outer part of the optic stalk and nerves to the retina (R) (after Bliss and Welsh, 1952); (*c*) post-commissure organ (Post. com.) of a prawn, *Leander*, attached to tritocerebral commissure and having neurosecretory granules, (after Knowles, 1955). Protocerebrum (PRO), carrying optic lobes (OP), and deuterocerebrum (DEU), both joined by internal commissures, not shown; tritocerebrum (TRI) with its commissure (Tr. com.) behind oesophagus (Oes); circumoesophageal connectives (Conn.) join brain longitudinally to fused suboesophageal (SUBOES) and thoracic ganglia (THOR). Eyestalk contains continuation of optic lobe ending in terminal medulla (MT) with ganglionic-X-organ (GXO), and neurosecretory axons that end in sinus gland (SG) on internal medulla (MI); the external medulla (ME) also has some neurosecretory axons. Nerve roots to antennae (A i and A ii), viscera (Vis), mandible (Mdb), maxillae (Mx i and Mx ii) and thoracic appendages (Th i, etc.).

in the brain still in place; removal of the sinus gland only (by means of a minute punch, like an apple corer; Kleinholz, 1947) leaves both sources undamaged and able to continue their secretion.

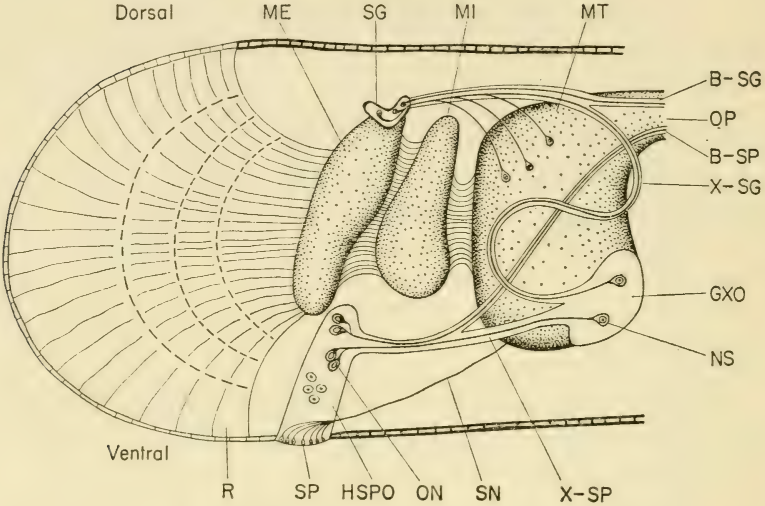

FIG. 2-6. Eyestalk of prawn, *Lysmata*, cut open in the vertical plane (cf. Fig. 2-5). Some neurosecretory cells in the ganglionic-X-organ (GXO) in the terminal medulla (MT) have axons which pass in a bundle (X–SG) to the SINUS GLAND (SG) on the dorsal surface of the external medulla (ME); others have axons (X–SP) that pass ventrally to HANSTRÖM'S SENSORY PORE ORGAN (HSPO) and end in "onion bodies" (ON). Both sinus gland and sensory pore organ also have axons (B–SG and B–SP respectively) from neurosecretory cells in the brain. The sensory pore retains some sense cells (SP) connected by a sensory nerve (SN) to the brain (from Carlisle, 1953).

In the Malacostraca with long eyestalks, the SINUS GLAND is usually on the dorsal surface of the optic ganglion, either on the internal or external medulla (Figs. 2-5*b* and 2-6). It is largely composed of an aggregate of swollen ends of the long neurosecretory cell axons from the brain and the ganglionic-X-organ; they converge on a half open cavity in communication with the adjacent blood sinus. In the blue crab, *Callinectes*, there is evidence that the sinus gland is composed of as many as five groups of axon endings, each with a distinctive staining reaction, which can be traced back along the axon (Potter, 1954). It seems highly probable that these groups are responsible for secreting and releasing most of the specific chemicals with different hormonal actions, which can be found by experiment in the sinus gland.

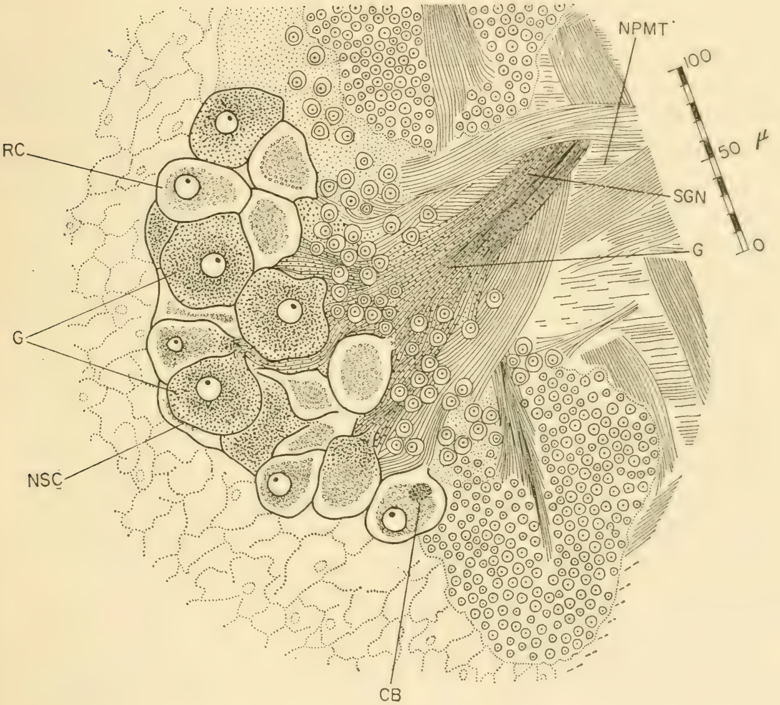

FIG. 2-7. Neurosecretory cells (NSC) in the ganglionic-X-organ of a crab, *Sesarma*. Stained granules of secretion (G) pass down the axons (SGN) to the sinus gland. Some cells (CB) have few granules, others (RC) are almost depleted of granules. Small ganglion cells and nerve fibres (NPMT) of the surrounding terminal medulla are also shown (from Enami, 1951).

It has been suggested that, in addition to acting as a storage-and-release organ for the neurosecretion, the walls of the sinus gland may include some secretory cells, but of this there is no clear evidence (Knowles and Carlisle, 1956). It seems more likely that active hormones are being set free here from the inactive carrier substance that travels down the axons.

In the sessile-eyed Malacostraca, such as the Isopoda, both the ganglionic-X-organ and the sinus gland itself lie within the head capsule (Amar, 1948).

Hanström's sensory pore organ

The sensory pore organ, like the sinus gland, is the storage-and-release organ for neurosecretory cells some of which are situated within the BRAIN and others in the GANGLIONIC-X-ORGAN. All the axons have their endings swollen into characteristic onion-shaped bodies in HANSTRÖM'S SENSORY PORE ORGAN, situated on the ventral surface of the eyestalk in Malacostraca (Fig. 2-6). In addition to these axon endings and to the sensory cells, which give their name to the organ, there are some small secretory cells confined within the organ, at least in *Lysmata* (Carlisle and Passano, 1953).

This structure was originally called the "X-organ" and was identified in several species by Hanström (1939) and his pupils; but since then, many workers have used the name X-organ for the neurosecretory cell bodies located in the terminal medulla. The modified name of ganglionic-X-organ is here used for this latter group of cells, from which in fact axons run to both the sinus gland and to Hanström's organ (Knowles and Carlisle, 1956).

Commissures and connectives

Active extracts have been obtained from many other parts of the crustacean nervous system besides the supraoesophageal "brain"; but as yet there is little indication of where any natural hormones, corresponding in their actions to these extracts, may be released into the blood stream.

The TRITOCEREBRAL (or antennal) COMMISSURE, which is a cross connection passing below the oesophagus between the tritocerebral parts of the brain (Fig. 2-5*a*), is particularly rich in chromactivating materials (§ 3.2) in many Decapoda. In the prawns, *Leander* and *Penaeus*, it has been shown (Knowles, 1953 and 1954) that the attached POST-COMMISSURE ORGANS are the swollen bases of nerves, some motor fibres of which pass to dorsoventral muscles; the two nerves have a cross connection and contain many neurosecretory fibres and secretory droplets and yield an active extract. Some of the cell bodies are in the commissure (Fig. 2-5*c*).

The CIRCUMOESOPHAGEAL CONNECTIVES and the thoracic and abdominal ganglia also yield extracts of varying activity, particularly in forms such as *Palaemonetes*, in which the ganglia are not fused in one mass.

Pericardial organs

In Decapoda and Stomatopoda there are some rather unusual neurosecretory axons in the pericardium. They are supported by larger nerve trunks and end blindly in networks of very fine branches spread over the venous openings from the gills; they are therefore exposed to the blood stream and appear to secrete into it one or more chemicals that increase the rate of the heart beat (§3.111). The position of the cell bodies of these PERICARDIAL ORGANS has not yet been found; but recent evidence indicates the presence of very fine granules in the fibrils, and experimental evidence for their secretory activity is good. Similar structures may also be present in Isopoda (Alexandrowicz, 1953).

2.113 *Neurosecretory systems and glands of Insecta*

The nervous system of Insecta has given rise to both neurosecretory cells and simple secretory cells which have lost any morphological signs of their nervous origin. The former occur within the central nervous system, mainly in the suboesophageal ganglion and the brain, and the latter in the corpora cardiaca.

The tritocerebral commissures and the circumoesophageal connectives, though similar in form to those of crustaceans, have not been shown to yield active extracts in insects.

Suboesophageal ganglion

Neurosecretory cells have been identified microscopically in the SUBOESOPHAGEAL GANGLIA of several insects, including some

Ephemeroptera (Arvy and Gabe, 1953) and Plecoptera, where their axons are connected anatomically to the ventral gland (Fig. 2-8). Experiments have shown that in higher insects the suboesophageal ganglion is the source of a kinetic chromactivating

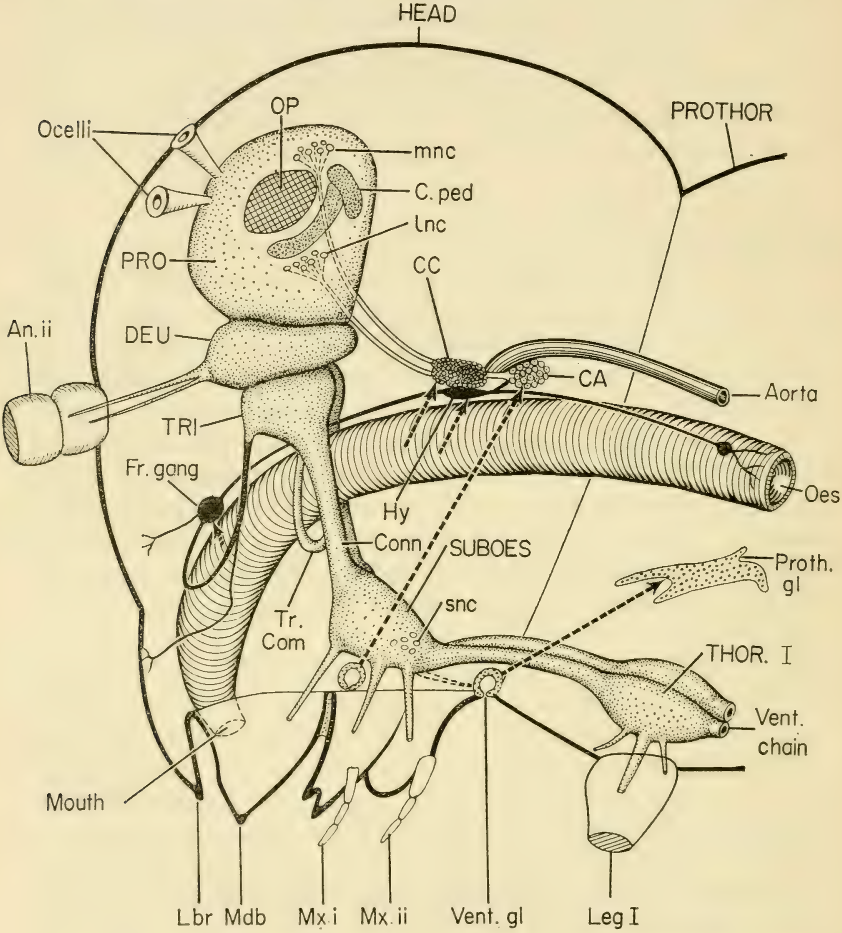
HEAD
OP
PROTHOR
Ocelli
mnc
C. ped
lnc
PRO
CC
An. ii
DEU
CA
Aorta
TRI
Fr. gang
Oes
Hy
Conn
SUBOES
Proth. gl
Tr. Com
snc
THOR. I
Vent. chain
Mouth
Lbr
Mdb
Mx. i
Mx. ii
Vent. gl
Leg I

FIG. 2-8. Central nervous system and sources of hormones in the head and prothorax of a hemimetabolous insect, in lateral view. The nervous system, with optic lobes (OP) cut off, resembles that of the crab (Fig. 2-5) and is similarly lettered and named, except that Mx ii is here the labium, and ganglia of the ventral chain are

hormone (§ 3.221) and of the metabolic diapause hormone (§ 5.112). In the cockroach, *Leucophaea*, these cells present a variety of appearances in fixed preparations (Fig. 2-2). These probably represent phases in secretion; but this has not been confirmed in the living animal.

Neurosecretory cells of the brain

Paired groups of neurosecretory cells are to be found in the brains of insects, as in crustaceans; but in most insects they appear to be confined to the PROTOCEREBRUM and not to extend into other parts of the brain or optic lobes. The neurosecretory cells usually lie in groups: the median neurosecretory cells (m.n.c., Fig. 2-3) lie anteriorly near the mid-line and other cells lie ventrally or laterally (l.n.c.). The former are connected to the corpus cardiacum of the opposite side by an internal nerve, and the latter by an external nerve (Fig. 2-8). Their axons lead into the CORPORA CARDIACA, where their secretion is stored (Fig. 2-9). The lateral neurosecretory cells may represent the frontal organs of Apterygota and may even be homologous with the cells of Hanström's sensory pore organ (§ 2.112). It is interesting to note that these groups of neurosecretory cells secrete endocrinokinetic hormones that stimulate endocrine glands in both Crustacea and Insecta (§ 4.21; Scharrer and Scharrer, 1954 *b*).

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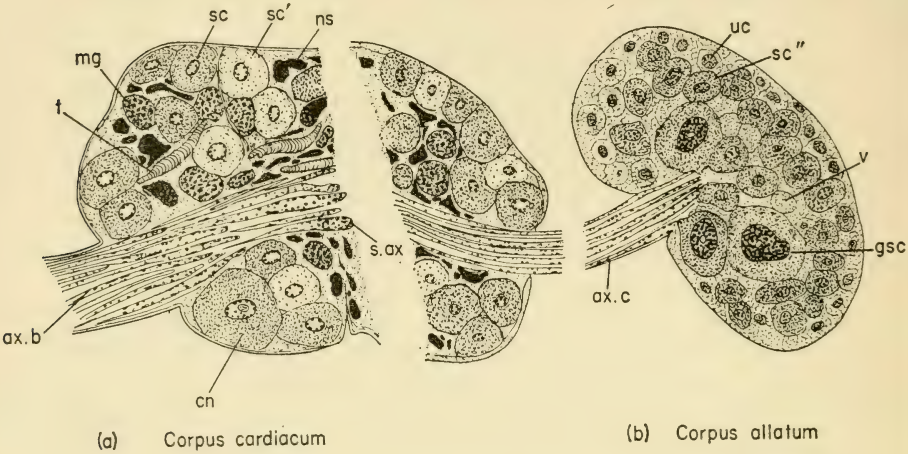
not fused. The stomatogastric, or visceral, nervous system arises from the stomodaeal ectoderm, and has paired nerves from the tritocerebrum, a median frontal ganglion (Fr. gang), a branch to the labrum (Lbr) and a recurrent nerve to the hypocerebral ganglion (Hy) and the paired ventricular ganglia on the gut (near Oes). HORMONES are secreted by median (m.n.c.), lateral (l.n.c.) and suboesophageal neurosecretory cells (s.n.c.); perhaps also by cells in paired corpora pedunculata (C.ped.). Secretions from these pass in two paired nerves to be stored in the CORPORA CARDIACA (CC), which arise from stomodaeal ectoderm (dashed arrow). Hormones are also secreted by two paired glands that arise as ectodermal invaginations: the CORPORA ALLATA (CA from Mx i), which migrate (dashed arrow) above the oesophagus, where they receive axons from the corpus cardiacum (cf. Fig. 2-9); and the VENTRAL GLANDS (Vent. gl. from Mx ii), which persist in primitive insects, but form prothoracic glands (Proth. gl.) in most other orders. (Based on two diagrams by Weber, 1949).

Storage of the neurosecretion from the brain in the corpora cardiaca has been conclusively shown in the cockroach, *Leucophaea*, where the system is paired (B. Scharrer, 1952). Unilateral section of the axons from the median neurosecretory cells results in the depletion of all stainable secretion from the corpus cardiacum of that side. At the same time, increased quantities of the secretion appear in the axons proximal to the cut (Fig. 3-2). The corpora cardiaca are nearly always fused with the dorsal blood vessel or aorta, into which they presumably pass the stored secretion as required (Hanström, 1940).



(a) Corpus cardiacum (b) Corpus allatum

FIG. 2-9. Sections of parts of (*a*) the CORPUS CARDIACUM of a beetle, *Hydrous piceus* (after de Lerma, 1956), and (*b*) the CORPUS ALLATUM of a grasshopper, *Melanoplus differentialis* (after Mendes, 1948). Axons (ax.b) from neurosecretory cells in the brain carry granules; some end in swellings (s.ax), like Herring bodies, and release masses of neurosecretion (ns) in the corpus cardiacum. Cells in different phases of secretion (sc and sc′) release masses of granules (mg) that stain with phloxin, and may be the intrinsic secretion of the organ. Tracheoles (t) and non-secreting nerve cells (cn) also occur. Other axons (ax.c) pass to the cells of the corpus allatum, where their granules disappear. It has undifferentiated cells (uc), secreting (sc″) and giant secreting cells with polyploid nuclei (gsc); acidophil granules pass with some fluid into intracellular vacuoles and are then extruded (v).

Gland cells of the corpora cardiaca

The CORPORA CARDIACA are not only storage organs for neurosecretion from the cerebrum but they are also endocrine organs in their own right. Together with the corpora allata (§ 2.122) they lie dorsal to the oesophagus and form the retrocerebral system (Fig. 2-8), the form of which varies in different insects; both organs may be paired, or one or both may be fused in the mid-line.

Together with some nerve cells, connective tissue and tracheae, loosely packed secretory cells form the bulk of the corpora cardiaca and produce the intrinsic secretion of this organ (§ 3.111). Like the sympathetic cells of the hypocerebral ganglion, these cells arise from the stomodaeal ectoderm and are undoubtedly nervous in origin, although they have become so much specialized for secretion that they have lost most of the characters of neurons, notably the axons of typical neurosecretory cells (Figs. 2-1*e* and 2-9*a*). These cells are rich in ribonucleic acid and reveal a Golgi apparatus after suitable treatment. With haematoxylin chrome phloxin, their secretion stains quite distinctively from the neurosecretion, the former having a greater affinity for phloxin and the latter for haematoxylin (de Lerma, 1956).

2.114 *Neurosecretory systems and glands of Vertebrata*

There are two main sources of hormones that are derived from the vertebrate nervous system. One is a set of neurosecretory cells in the hypothalamus of the brain with their storage-and-release organ (akin to the sinus gland of the Crustacea) in the neurohypophysis. The other is an aggregation of gland cells that are derived from sympathetic ganglia and form the suprarenal body of fish and the adrenal medulla of tetrapods.

Neurosecretory cells of the hypothalamus and the neurohypophysis

It is now well established that the hormones of the neurohypophysis (or posterior lobe of the pituitary body) are not secreted within that body but by neurosecretory cells in the hypothalamus of the brain. The cell bodies are grouped together in the preoptic nucleus in fish and amphibians and separated into two groups, the supraoptic and paraventricular nuclei, in reptiles, birds and

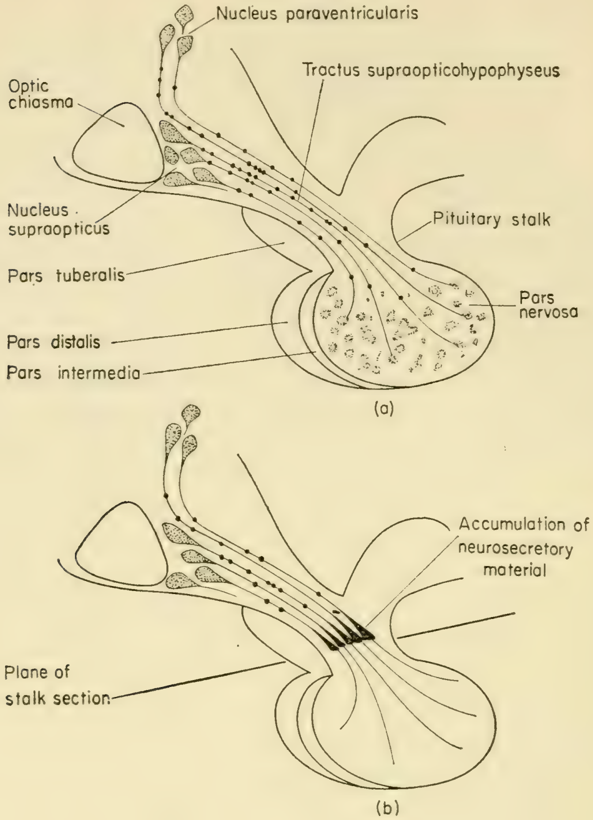

Nucleus paraventricularis
Tractus supraopticohypophyseus
Optic chiasma
Nucleus supraopticus
Pituitary stalk
Pars tuberalis
Pars nervosa
Pars distalis
Pars intermedia
(a)
Accumulation of neurosecretory material
Plane of stalk section
(b)

FIG. 2-10. Diagram of the pituitary body of a dog, *Canis*; (*a*) before and (*b*) after the pituitary stalk has been cut. Neurosecretory cells in the paraventricular and supraoptic nuclei of the hypothalamus of the brain pass secretory granules down their axons to the neural lobe of the neurohypophysis (pars nervosa), where they are stored in Herring bodies, or swollen axon endings, and thence pass into the surrounding blood vessels (Fig. 2-12). After cutting across the stalk, the neurosecretion accumulates in the proximal part of the axons and the supply previously accumulated in the neurohypophysis becomes depleted after a time and is not replenished. The pars distalis of the adenohypophysis (and pars tuberalis) lie in front of the pars nervosa, separated from it by the pars intermedia (from Scharrer and Scharrer, 1954*a*).

mammals (Fig. 2-10; Scharrer and Scharrer, 1954*a*). Unlike most neurosecretory cells of the arthropods, those of the hypothalamus of vertebrates possess dendrites (Fig. 2-1*b*).

In fish and aquatic Urodela their axons are not well developed and their function is uncertain; but in all terrestrial vertebrates from the terrestrial Urodela and Anura upwards the axons pass down the infundibular stalk to end in an enlarged neural lobe (pars nervosa). This becomes distinct from the median eminence at the base of the infundibulum and is not present in the lower forms (Fig. 2-11). In the course of evolution, the neural lobe has acquired an independent blood supply from the internal carotid arteries, forming a relatively rich vascular network (Fig. 2-12) with which the axons of the neurosecretory cells make contact by their swollen endings, called Herring bodies, similar in appearance to those of the comparable cells in the crustacean sinus gland. They can be shown by appropriate staining to be filled with neurosecretory granules. In mammals the secretory granules first become visible in the embryo, where they appear to be carriers for the actual hormones released from the neurohypophysis. The relation between secretion and hormone formation has now been as clearly shown here as anywhere, although the proofs were obtained later than in the invertebrates. In any vertebrate from fish to mammals, section of the axons in the infundibular stalk results in accumulation of the secretion in the parts proximal to the cut and its depletion beyond; and the possibility of obtaining active extracts from the different parts of the system follows the same pattern. It has also been possible to grow cells from the supraoptic nucleus of a dog in tissue culture and to observe (and even to make a ciné film of) the secretory granules passing from the cell body down the axon.

The neurohypophysis therefore acts as a storage-and-release organ for the hypothalamic secretion or secretions. Two distinct hormones have been recognized, the antidiuretic hormone and oxytocin, but there does not seem to be any constant arrangement of the neurosecretory cells which produce them. In the dog, for instance, both substances can be obtained from both supraoptic and paraventricular nuclei, although the proportion of oxytocin to the antidiuretic fraction is always small; but in the camel, oxytocin

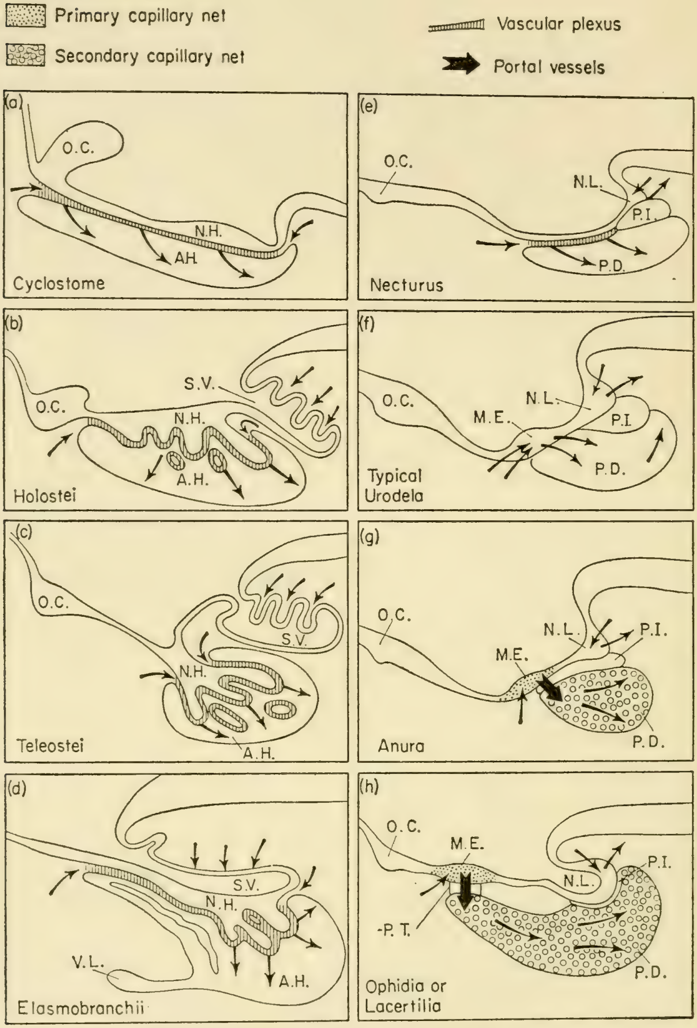

Primary capillary net
Secondary capillary net
Vascular plexus
Portal vessels
(a)
O.C.
N.H.
AH
Cyclostome
(e)
O.C.
N.L.
P.I.
P.D.
Necturus
(b)
S.V.
O.C.
N.H.
A.H.
Holostei
(f)
O.C.
N.L.
M.E.
P.I.
P.D.
Typical
Urodela
(c)
O.C.
S.V.
N.H.
A.H.
Teleostei
(g)
O.C.
N.L.
P.I.
M.E.
P.D.
Anura
(d)
S.V.
N.H.
V.L.
A.H.
Elasmobranchii
(h)
O.C.
M.E.
P.I.
N.L.
-P.T.
P.D.
Ophidia or
Lacertilia

FIG. 2-11. Pituitary body in diagrammatic sagittal section with its circulation shown by thin arrows: *a* to *d* in fish, *e* to *h* in amphibians and reptiles. A.H., adenohypophysis, divided into pars distalis (P.D.), pars tuberalis (P.T.), and pars intermedia (P.I.) in tetrapods; N.H., neurohypophysis, divided into median eminence (M.E.) and neural lobe (N.L.) with separate circulation

is the more abundant in the paraventricular nucleus (Van Dyke, Adamsons and Engel, 1957).

These hormones are concerned with counteracting thirst and the desiccation that is the main risk accompanying the migration from water to land. The antidiuretic hormone facilitates reabsorption of water from the urine (§ 5.322) and oxytocin increases the excretion of Na^+ and Cl^- (§ 5.312). It is therefore understandable that the neural lobe, where these hormones can be quickly released into the blood, should be best developed in terrestrial animals (Harris, 1955). The correlation has been confirmed by the observation that natural thirst, or an equivalent state caused by injecting rats with saline, is followed by depletion of the secretory granules within a few minutes, to be slowly replaced in a day or so after giving the animals water to drink. Depletion of secretory granules in fish has been observed in response to immersion in hypertonic sea water, which would have the same effect as desiccation (Arvy, 1957).

Gland cells of the suprarenal tissue and adrenal medulla

The peripheral neurons of the sympathetic nervous system all secrete adrenaline, or noradrenaline, at their motor nerve endings. In most vertebrates some of these neurons become modified to secrete relatively enormous amounts of either or both of these substances; at the same time the cells lose all histological resemblance to ganglion cells (Fig. 2-1*f*). Their origin and function is nevertheless the same as that of neurosecretory cells; but opinion is divided as to whether they should be regarded as such (Welsh, 1955). They are often referred to as "chromaffin" cells, because the contained adrenaline gives a characteristic olive-brown colour with any chromic salts used either as fixative or stain. Staining shows that the adrenaline is secreted by the cytoplasm as a mass of very fine granules.

In fish, where these cells form the "suprarenal" tissue, they

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in most tetrapods. Heavy arrows indicate the presence of portal veins between primary venous plexus in median eminence and secondary plexus in pars distalis (cf. Fig. 2-12) in fully terrestrial forms. O.C., optic chiasma; S.V., saccus vasculosus; V.L., ventral lobe (from Green, 1951).

remain in their original paired positions and are innervated by the preganglionic fibres of the visceral motor or sympathetic system. They secrete mainly noradrenaline.

From Amphibia to Mammalia this tissue, having migrated towards the anterior ends of the kidneys, becomes progressively enveloped in the interrenal or cortical tissue, derived from coelomic epithelium (§ 2.311). The chromaffin tissue forms the adrenal medulla, or core, and secretes mostly adrenaline in mammals. Together, the cortex and medulla form the complex adrenal gland.* The cells of the medulla are innervated in the same way as in fish. Some unmodified ganglionic cells may be seen among them; but the chief characteristic of the tissue is the network of blood spaces with which every cell is in contact and into which their secretion can be passed with great rapidity in response to nervous stimulation in an emergency (§ 3.11).

2.12 ENDOCRINE GLANDS DERIVED FROM ECTODERMAL EPITHELIUM

A number of endocrine glands are derived from ectodermal epithelium, without having any apparent connection with the nervous system. These seem to be more frequent in invertebrates than in vertebrates, and include the Y-organ and the prothoracic glands, which are the main sources of the morphogenetic moulting hormones of Arthropoda (§ 4.21 and Part II). The salivary glands of Cephalopoda may be included here (§ 2.121), although it is doubtful if their secretion is a true hormone. The corpora allata of Insecta (§ 2.122) and the adenohypophysis of Vertebrata (§ 2.123) are both important ectodermal sources of kinetic and metabolic hormones.

2.121 *Salivary glands of Cephalopoda*

Salivary glands of cephalopods are primarily used for the external secretion of tyramine, a poison for immobilizing the prey;

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* Unfortunately, in medical terminology, this compound gland is usually referred to as the "suprarenal", from its position "above" the kidney in the upright posture. It must not be confused with the suprarenal of fish, which is homologous with the medulla only.

but this substance also passes into the blood, to affect the chromatophore muscles (§ 3.21), probably by an indirect action.

The glands, of which there are two in decapod and four in octopod cephalopods, arise from the stomodaeal ectoderm, with which they retain their connection as a duct to the mouth. It is the posterior (or dorsal) pair which secretes tyramine in *Eledone moschata* and in the two species of *Octopus* which have been investigated (Bacq and Ghiretti, 1951).

2.122 *Corpora allata of Insecta*

The CORPORA ALLATA are endocrine glands, the cells of which arise in development as a pair of small ventrolateral invaginations near the base of the first maxilla (Fig. 2-8). Thence the tissue migrates inwards to lie between the oesophagus and the aorta; it may remain paired, or the two parts may fuse more or less completely. Each part is supplied with neurosecretory axons passing on from the corpora cardiaca, which lie just in front of them (Fig. 2-9).

There is evidence that these axons must remain intact if they are to control secretion by the corpora allata, as though their action were either nervous or due to a neurohormone diffusing from cell to cell rather than being carried in the circulation. The corpora allata are also connected with the stomatogastric system by nerves from the hypocerebral ganglion.

The densely packed cells of the corpora allata show cyclic phases of secretion and multiplication, coinciding with their cyclic activity in controlling the "juvenile" character of nymphal and larval moults (Part II, § 3). A new phase of activity starts very soon after each moult is completed: at first the gland is small and the cells are all alike; then there is a burst of mitotic activity followed by an increase in size of some cells, leading to increase in gland size. The larger cells, which have much larger nuclei than the undifferentiated cells, then begin to form their secretion. This appears first as granules in the cytoplasm; it then accumulates in vacuoles, which can later be seen to lie outside the cells in intercellular spaces. From this position the secretion, or the hormone released from it, presumably passes into the blood stream at the critical period for controlling the next moult. Some of the secreting cells become polyploid by division of their nuclei without cell division. They form giant cells (g.s.c., Fig. 2-9). When secretion is completed, the gland returns to the initial undifferentiated state shortly before the actual moult (Mendes, 1948). The glands also secrete metabolic (§ 5.11) and morphogenetic hormones (Part II, § 3) during the adult life of the insect, when the histology of secretion appears to be the same as that in younger stages, and gives no indication of the hormones being different at different ages.

2.123 *Adenohypophysis of Vertebrata*

The adenohypophysis, or the anterior lobe of the pituitary body, is the only endocrine gland which arises from non-nervous ectoderm in vertebrates. Its origin is the hypophysis, an upgrowth from the roof of the stomodaeum. It meets the brain and induces a downgrowth from the hypothalamus or floor of the diencephalon; together they form the pituitary body (Fig. 2-13). Throughout the vertebrates the contribution from the nervous system forms the neurohypophysis which has already been described (§ 2.114).

The subdivisions of the ectodermal ADENOHYPOPHYSIS are difficult to homologize in different groups. It has recently been recommended (Pickford and Atz, 1957) that the noncommittal terms pro-, meso- and meta-adenohypophysis should be used for fish and that these should only be very tentatively homologized with the three parts recognizable in most tetrapods, namely the PARS TUBERALIS, the PARS DISTALIS and the PARS INTERMEDIA (Fig. 2-10).* Of these, the pars distalis is usually the largest and appears to be the main source of hormones. It lies in front of the original hypophysial cavity, or cleft, if this persists, whereas the pars intermedia forms behind the cleft and often comes into close contact with the adjacent neural lobe. The pars tuberalis surrounds the infundibular stalk. The shapes and relative sizes of these parts vary greatly in different animals (Fig. 2-11). The pars distalis becomes increasingly important in land animals, and especially in mammals, whereas the pars intermedia decreases in size and may even be wholly lacking, as in the chick and whale.

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* Unfortunately, the old nomenclature is still to be found in many books; in this, the pars intermedia, although formed from the same tissue as the rest of the adenohypophysis or "anterior lobe of the pituitary", is included with the pars nervosa in the so-called "posterior lobe of the pituitary"; this is due to its morphological position in some mammals. Other writers use posterior lobe as synonymous with the neural lobe, or pars nervosa, only (Fig. 2-10). The names used here follow those recommended by the International Congress of Anatomists (Woerdeman, 1957).

The blood supply of the pituitary also shows important differences in different classes of vertebrates (Fig. 2-11). In fish, hypophysial arteries from the internal carotids break up into a vascular plexus, which penetrates the whole organ and eventually drains into venous sinuses under the skull. (The saccus vasculosus may have a separate supply; but it is not part of the endocrine gland.) In Urodela, the arterioles pass first to the pars tuberalis and thence to the capillary plexus of the pars distalis and pars nervosa. The pars intermedia hardly has any share in the blood supply.

In the Anura and amniotes, the plexus in the pars tuberalis penetrates into the median eminence and then the vessels join up to form a number of portal veins which break up into a secondary venous plexus in the pars distalis (Fig. 2-11 *g* and *h*). It might be thought that this portal system was less important in mammals than in lower forms, since in them alone the pars distalis acquires a direct arterial blood supply from the internal carotids (Fig. 2-12); but it may allow the passage of *CRF* (§ 4.323). In all land animals the newly developed neural lobe of their neurohypophysis also acquires an independent arterial supply from the same source. These vessels from the neural lobe, together with all those from the pars distalis, drain into the same venous sinus and eventually join the internal jugular veins.

Nerve axons to the pituitary fall into two distinct categories: those of neurosecretory cells, and those of sympathetic nerves. The neurosecretory cells are confined to the neurohypophysis, and most of them end in the neural lobe; but some of them make contact with the primary venous plexus in the median eminence. In this way, secretions from the latter can pass into the portal circulation and so to the pars distalis. How much they do so, and whether they affect the rates of hormone secretion from the adenohypophysis, is still a matter for discussion.

The vasomotor fibres of the sympathetic nerves follow the course of the hypophysial arteries (Fig. 2-12); they can therefore

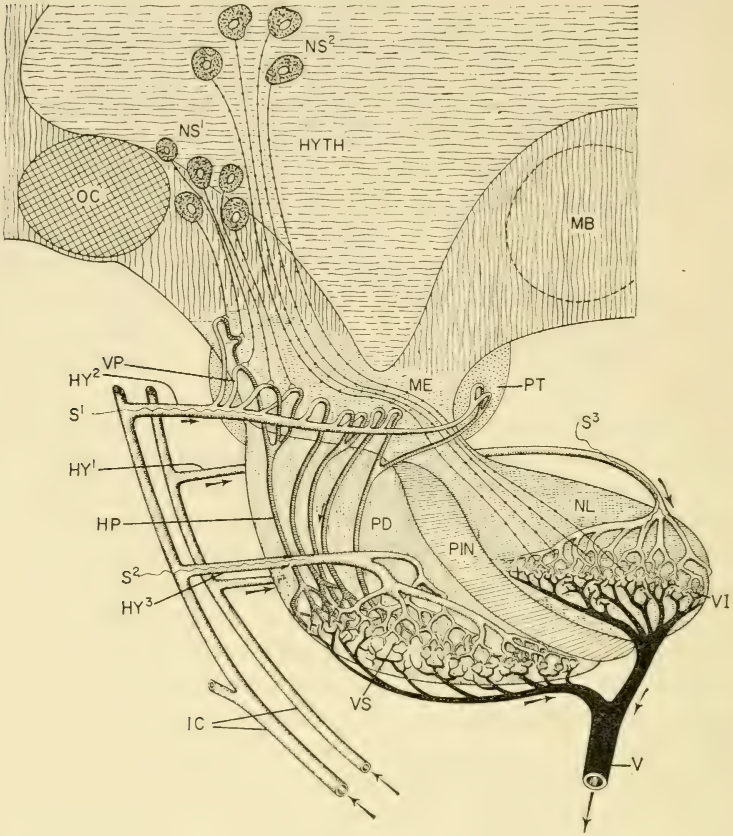

FIG. 2-12. Diagrammatic sagittal section of the pituitary gland and hypothalamus of a rabbit, *Oryctolagus*, with the circulation superimposed and simplified. The neurosecretory cells (NS¹ and NS²) have been disproportionately magnified to show their axons connecting with the primary plexus of veins (VP) in the median eminence (ME) and (VI) in the neural lobe (NL). The only other nerves are sympathetic vasomotor fibres (S¹, S² and S³). Blood comes from the internal carotids (IC) by hypophysial arteries; the upper right (HY¹) takes an independent supply to the NEURAL LOBE (NL), which is drained by the main vein (V). The PARS INTERMEDIA (PIN) has practically no circulation. The upper left hypophysial artery (HY²) supplies the primary venous plexus in

control the blood supply to the neural lobe and the pars distalis, but do not appear to make any contact with the secretory cells.

There are no nerves to the pars intermedia in mammals, though secretions from this part appear to be under nerve control in fish and amphibia (§ 4.3).

The PARS DISTALIS of the adenohypophysis contains at least three distinct types of cells: *chromophobe* (gamma) cells which have no stainable granules in their cytoplasm and seem to have no secretory function, though they may give rise to one or both of the secreting types; *basophil* cells, which contain secretory granules of glycoprotein that stain blue by the Mallory or Azan trichrome methods, and *acidophil* cells, which contain phospholipid granules that stain selectively by an acid haematin method. The last two types can also be distinguished by staining with safranine-acid violet (cf. Maximow and Bloom, 1942, Fig. 261.-2) and show changes which are clearly associated with the secretory activity of the gland. For some time it was claimed that only these two types of secreting cells could be identified histologically although the gland was known to secrete six or seven distinct hormones; but recently more sensitive tests have been applied and tentative subdivisions of the two types have been proposed (Table 4); further details have recently been summarized by Pickford and Atz (1957).

The PARS TUBERALIS has not been studied so fully but appears to consist of columns of cells separated by blood spaces, and to be closely similar to the adenohypophysis in appearance. A secretory activity has only been claimed for it in some fish and amphibians (§ 3.23).

The PARS INTERMEDIA may consist of cells with basophil granules and non-granular cells that form follicles filled with a colloid, similar in appearance to that in the thyroid gland but containing

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the PARS TUBERALIS (PT), from which loops penetrate deeply into the median eminence and can receive neurosecretions. These vessels join again to give the hypophysial portal system (HP) which breaks up into the secondary venous plexus (VS) in the PARS DISTALIS (PD) of the adenohypophysis. This part also receives blood directly from the lower hypophysial arteries (HY^3). (Original, based on Scharrer and Scharrer, 1954*a*; and Harris, 1955).

TABLE 4. CELLS IN THE PARS DISTALIS OF THE ADENOHYPOPHYSIS

CELLS	STAIN	SECRETION	SECTION NO.
Basophil cells			
beta	*PAS*† and aldehyde fuchsin	TSH*	4.221
delta	*PAS* only, peripheral ?	FSH	4.232
,,	,, ,, central ?	LH	4.232
?	—	ICSH ?	4.232
Acidophil cells			
alpha	Orange G	STH	4.223
epsilon	Fuchsin	LSH	4.232
?	—	ACTH	4.231

* See glossary.

† *PAS* = Periodic acid–Schiff method, with which these cells give a positive reaction.

no iodine. This region is well known to secrete a melanophore dispersing hormone, intermedin, in many fish and most amphibians, but not in Agnatha. It has also been claimed that this lobe may act as a storage-and-release centre for adrenocorticotrophin, ACTH (Mialhe-Voloss, 1955). The claim may be due to the chemical identity of intermedin with a large part of the chain molecule that makes up ACTH.

2.2 ENDODERMAL SOURCES IN VERTEBRATA

Hormones secreted from endodermal sources have so far only been recognized in vertebrates. They fall into two categories: isolated cells in the stomach and intestinal mucosa (§ 2.21) and well-developed endocrine glands in the pharynx and pancreas (§ 2.22). The former secrete kinetic hormones which control gut muscles and the secretion of digestive enzymes from exocrine glands; the latter secrete various metabolic hormones (Table 5).

2.21 ISOLATED CELLS IN THE GUT

A large number of hormones can be located in the stomach and intestine of mammals; some of these also occur in birds, but they are not known to be active in cold-blooded vertebrates.

Since no recognizable endocrine glands or groups of secreting cells have been found in the GUT MUCOSA in those regions from which the gastrointestinal hormones, such as GASTRIN and SECRETIN, can be extracted (§ 4.11), it must be concluded that all these hormones arise from isolated cells (Table 5). So far, however, these cells have not been found, despite intensive search; it is possible that they may not be histologically distinct from other cells in the gut lining, such as those secreting mucus, but it seems more likely that they will eventually be revealed by more sensitive or selective staining techniques. It has been suggested that SECRETIN may be produced in certain "argentaffine" cells, which can be stained with silver; but this seems unlikely since similar cells are abundant in the vermiform appendix from which no secretin can be extracted (Grossman, 1950).

The origin of the secretory cells certainly deserves further investigation. The clues that would seem to be the most worth following are the facts that (1) the action of this whole group of hormones is kinetic, (2) all other kinetic hormones come either from modified nerve cells or at least from the ectoderm and (3) the action of these hormones in stimulating the secretion of stomach, pancreas and intestinal glands is carried out in lower vertebrates by the parasympathetic nerves in the vagus. The parasympathetic nerves form part of the general visceral motor system and like the sympathetic nerves have peripheral ganglia, connected to the brain by preganglionic fibres. The latter are of central nervous origin; but there is considerable doubt as to the origin of the peripheral cells, though the neural crest has been plausibly postulated. If so, crest cells might be expected to migrate to the intestine from the cranial region to form ganglia; and it seems possible that some of them might also form argentaffine cells, and others secretory cells. Although there is evidence that the argentaffine cells of the gut can differentiate in grafts of chick intestinal epithelium, even if this is separated from the embryo before any trunk neural crest material is formed (Van Campenhout, 1946), it is not so clear that cranial neural crest cells were excluded in these experiments. On the other hand, there is one other curious feature about all the hormones secreted by the gut wall in mammals: unlike kinetic hormones derived from neurosecretory cells, they are not secreted in response to nervous stimulation, but always depend upon a direct stimulus, either mechanical or chemical (§ 4.321).

The positions from which the various hormones have been found to be secreted in the gut are summarized in Table 5.

TABLE 5. ENDODERMAL SOURCES OF KINETIC AND METABOLIC HORMONES IN VERTEBRATA

CLASS	SOURCE OF HORMONE	NAME OF HORMONE	TYPE OF ACTION *	SECT. NO.
2.21 ISOLATED CELLS IN THE GUT				
Mammalia	Stomach	Gastrin	K	4.111
,,	Duodenum	Cholecystokinin	K	3.112
,,	,,	Secretin	K	4.111
,,	,,	Pancreozymin	K	4.111
,,	,,	Duocrinin	K	4.111
,,	Intestine	Enterocrinin	K	4.111
,,	,,	Enterogastrone	K	4.112
2.22 ENDODERMAL ENDOCRINE GLANDS				
2.221 *Glands of the pharynx*				
Agnatha to *Mammalia*	Thyroid	Thyroxine	M	5.111
Teleostei	Ultimobranchial body	Parathormone	M	5.411
Tetrapoda	Parathyroid	,,	M	5.411
,,	,,	,,	M	5.422
2.222 *Gland cells in the pancreas*				
Agnatha to *Mammalia*	Islets of Langerhans	Insulin	M	5.212
Aves and some *Mammalia*	,,	Glucagon	M	5.211

* K = kinetic. M = metabolic.

2.22 ENDODERMAL ENDOCRINE GLANDS

Recognizable endocrine gland cells are derived from the gut epithelium in two regions: the pharynx, where there are at least two groups (§ 2.221), and the pancreas, where they form the islets of Langerhans (§ 2.222). These glands all secrete metabolic hormones, and their structure has long been known; it is well described in most text-books of vertebrate anatomy, embryology and histology, and little need be said here, except to emphasize the fact that they can be identified in most classes of vertebrates and are not confined to the warm-blooded forms, like the sources of the gastrointestinal hormones.

2.221 *Glands of the pharynx*

These are the THYROID and PARATHYROID GLANDS and the ULTIMOBRANCHIAL BODIES, which are the homologues of the parathyroids (Table 5). The thymus glands also arise here (Fig. 2-13); but their endocrine nature is uncertain. It will be considered in relation to growth (Part II, § 3).

Thyroid glands

In Agnatha, the endostyle in the floor of the larval pharynx can accumulate iodine, and even synthesize THYROXINE, albeit in small quantities, even before its transformation to the adult thyroid gland. The endostyle of the amphioxus, *Branchiostoma*, also accumulates iodine; but it does not appear to synthesize thyroxine (Barrington, 1958). It is then possible to argue either that the endostyles of the Protochordates and the Agnatha are homologous with each other and with the thyroid gland, because the former are structurally similar although only the two latter have acquired the ability to synthesize thyroxine, or that a true homology should be marked by similar chemical activities, and is in this case limited to the vertebrates.

The thyroid gland retains its position as a single median organ in the floor of the pharynx in lower vertebrates (Fig. 2-13) where the gland itself may be diffuse, as in many teleost fish, or relatively compact and enclosed in a capsule of connective tissue, as in Elasmobranchii and a very few Teleostei, such as *Pseudoscarus*, from which it can therefore be relatively easily removed. In tetrapods, in which the gills are lost, the gland often becomes paired and may even be further subdivided; but each part is

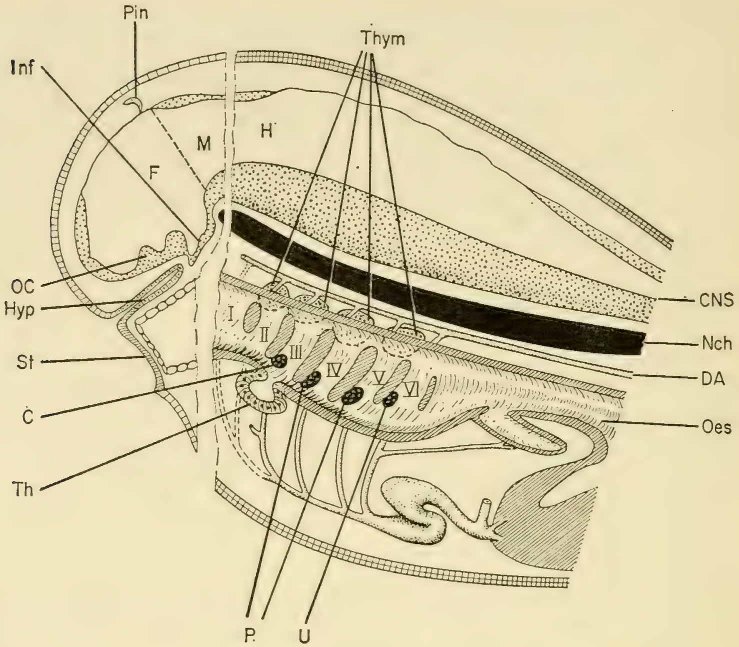

FIG. 2-13. Diagrammatic sagittal half of the head and pharynx of a tadpole, *Rana*. An *early stage* in development of the brain and stomodaeum (St) shows the ADENOHYPOPHYSIS (Hyp) growing up to meet the infundibulum (Inf), or NEUROHYPOPHYSIS, from the floor of the fore brain (F); together they form the pituitary body. Optic chiasma (OC), pineal organ (Pin), spinal cord (CNS) and notochord (Nch). The pharynx, leading to oesophagus (Oes), is shown at a *later stage*; I to VI, visceral arches; III to VI with branchial arteries running behind gill slits to dorsal aorta (DA); THYROID (Th) is mid-ventral; a series of ventrolateral epithelial thickenings form the carotid gland (C) on III, the PARATHYROIDS (P) on IV and V, and the ULTIMOBRANCHIAL BODY (U) on VI. Dorsolateral thickenings on II and III (and also on IV and V in other animals) form the THYMUS GLAND (Thym).

compact and encapsuled. It receives a rich blood supply from the carotids, and its nerve supply is mainly vasomotor.

In most vertebrates the histological character of the gland is fairly constant. Its cells form a cubical epithelium surrounding spaces, which become filled with a colloidal material secreted into it as droplets from the cells (Figs. 2-14*a* and 4-7). This appears to be a precursor of the hormone, usually in the form of diiodotyrosine; it is later reabsorbed into the cells, converted to thyroxine, and passed into the blood as the hormone (Fig. 4-8). This process is described more fully in relation to its control by the thyrotrophic hormone, TSH (§ 4.221).

Ultimobranchial bodies

These structures arise ventrolaterally from the epithelium of the last gill slit and may be seen in development to give rise to a pair of small glands. In fish they appear to replace the parathyroid glands; but in tetrapods they may be present in addition to them (Fig. 2-13). In function they appear to be similar to the parathyroids (§ 5.4).

Parathyroid glands

These glands are serially homologous with the ultimobranchial bodies behind (and with the so-called carotid gland of Amphibia in front). They arise ventrolaterally from the epithelium lining the gill slits on the anterior surfaces of the fourth and fifth visceral arches (Fig. 2-13).

The individual cells of the parathyroid glands form a densely packed mass amid ramifying blood vessels, and are not arranged in follicles. They may be of two kinds: the more numerous have clear cytoplasm and relatively large nuclei; the rest are acidophil with granular cytoplasm. The former are thought to be the main source of PARATHORMONE (§ 5.4).

2.222 *Gland cells in the pancreas*

In most vertebrates, groups of endocrine cells occur among the exocrine cells (secreting enzymes and alkali) in the pancreas; they form the ISLETS OF LANGERHANS. In larval lampreys these endocrine cells lie adjacent to the rest of the pancreatic tissue, and only become embedded within it in the adult. The endocrine cells are distinguishable histologically because they stain much less readily than the surrounding exocrine gland cells. This is due to the constant presence of so-called *beta* (β) cells that secrete the antidiabetogenic hormone, INSULIN (§ 5.212). These cells have very fine granules only, and have little affinity for any cytoplasmic stains. In at least some of the higher vertebrates, and especially in such mammals as the cat and dog, two other types of cell can also be distinguished in the islet tissue. Of these, the *alpha* (α) cells secrete the diabetogenic hormone GLUCAGON (Table 5); they contain large granules that stain bright red with Mallory-azan stain, but their cytoplasm also has little affinity for any stains. The D type of cell in the islets stains blue in the same preparation, but its function is unknown (Fig. 2-14*b*; Maximow and Bloom, 1942).

2.3 Mesodermal sources in Vertebrata

Metabolic hormones secreted by mesodermal sources have so far only been found in vertebrates. These come from the adrenal cortex and its homologue, the interrenal tissue. Other hormones from the mesoderm are all morphogenetic in their actions, or predominantly so; their sources, including the source of progesterone (despite the possible kinetic activities that have been attributed to this hormone in § 4.12), will be described in Part II.

2.31 ENDOCRINE GLAND CELLS DERIVED FROM COELOMIC EPITHELIUM

In all vertebrates the coelomic epithelium in the region of the kidneys gives rise to characteristic yellow gland cells, filled with fat and secreting cortical sterolic hormones. The cells are homologous in all classes; but they are differently named according to their positions. In fish they often retain their median position between the kidneys, where they form interrenal tissue, or they may become paired, as in the perirenal organs of Dipnoi. In the tetrapods the tissue forms the adrenal cortex; it is always paired, lies in front of the kidneys, and becomes closely associated with the adrenal medulla during development. The cortex finally encloses the medulla completely in mammals (Table 6).

2.311 *Interrenal tissue*

In Elasmobranchii, cortical gland tissue occurs as one or more median yellow masses, the interrenal tissue, so-called from its position between the kidneys. It is widely separated from the paired groups of suprarenal cells which represent the adrenal medulla of higher forms.

In Teleostei and related bony fish, the homologous tissue is called the anterior interrenal body, to distinguish it from the corpuscles of Stannius, or posterior interrenal bodies. The former resembles the adrenal gland of tetrapods, in containing a mixture of typical cortical and medullary cells. Of these, the cortical cells respond to stimulation by the adrenocorticotrophic hormone, ACTH, from the pituitary. Like the interrenal cells of the elasmobranchs, this tissue yields an active extract which is interchangeable with that of any tetrapod adrenal cortex. Injection of any of the extracts can keep alive a mammal or bird from which the cortex has been removed.

TABLE 6. MESODERMAL SOURCES OF METABOLIC HORMONES IN VERTEBRATA

CLASS	SOURCE OF HORMONE	NAME OF HORMONE	TYPE OF ACTION*	SECT. NO.
2.31 ENDOCRINE GLANDS FROM COELOMIC EPITHELIUM				
Elasmobranchii	Interrenal tissue	Cortical hormone	M	5.311
Teleostei	Anterior ,, ,,	,, ,,	M	5.311
	(& corpuscles of Stannius ?)	,, ,,	M	5.321
Tetrapoda	Adrenal cortex	,, ,,	M	5.112
,,	,, ,,	,, ,,	M	5.211
,,	,, ,,	,, ,,	M	5.223
,,	,, ,,	,, ,,	M	5.412
,,	,, ,,	,, ,,	M	5.421
,,	,, ,,	Aldosterone-like	M	5.311
,,	,, ,,	Hydrocortisone-like	M	5.321

* M = metabolic.

The corpuscles of Stannius are small, paired globules of tissue, embedded in the mesonephric kidneys; there are numerous pairs in *Amia*, but most teleosts have only one pair. Histologically their cells look like cortical tissue; but they do not seem to respond to ACTH, and their function is uncertain. Their homology with true interrenal tissue is also in doubt, since they appear to arise from the pro- and meso-nephric ducts, and not from coelomic epithelium (cf. Pickford and Atz, 1957).

2.312 *Adrenal cortex*

Like the interrenal tissue, the adrenal cortex is a small mass of conspicuous yellow tissue; but it is paired and situated in front of, or below, the kidneys, whether these are mesonephric or metanephric. The colour is due to large amounts of fat enclosed in the cells and associated with the formation of the sterolic hormones secreted by the gland. The presence of stored hormone in the gland is also related to the presence of ascorbic acid, which becomes depleted when the hormone is passed into the blood stream in response to some form of stress (§ 4.231 and Fig. 4-9), and to release of ACTH.

Three layers can usually be recognised in the cortex: an outer layer (just within the connective tissue capsule enclosing the whole gland), where active cell multiplication follows the frequent nuclear mitoses; a thicker middle region of actively secreting cells; and the innermost layer, next to the medulla, where the cells become degenerate and are eventually consumed by macrophages from the blood. It seems that throughout the life of the gland, cells are formed near the outer surface, migrate inwards during their secretory phase and are then destroyed as they reach the inner surface.

The main secreting cells of the cortex form a compact mass or continuum, in which the individual cells tend to be polyhedral, from contact with adjacent cells (Fig. 2-14*c*). In the rat, the mass is tunnelled through by a network of blood sinusoids, so abundant that every cell has a facet in contact with a blood vessel into which its secretion can be passed (Pauly, 1957; Fig. 2-15).

The structural details of the gland, and the proportion of connective tissue to gland cells, varies from species to species; but this has not been shown to have any effect upon the functional activity of the gland. No nerves have been detected.

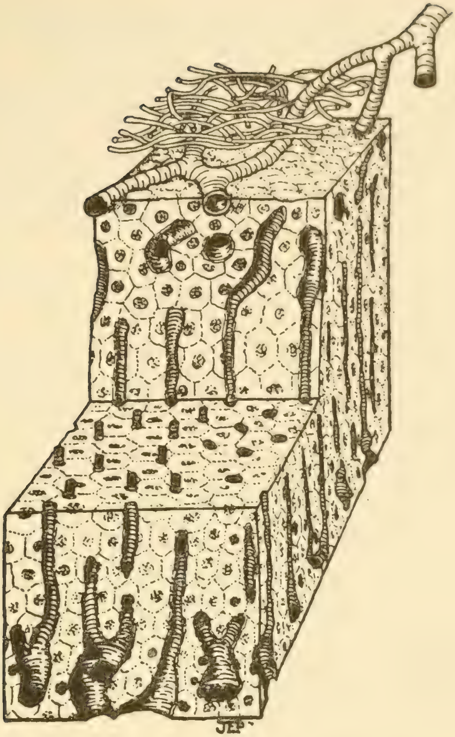

FIG. 2-15. Stereogram of part of the ADRENAL CORTEX of *Rattus*; the cells form a continuum through which blood capillaries tunnel to make contact with each cell. The fibres on the outer (upper) surface represent the connective tissue capsule surrounding the gland; below this, the blood vessels branch freely and then run directly inwards through the main secretory region (zona fasciculata) of the gland and anastomose at the inner (lower) surface, next to the medulla (which is not shown). (From Pauly, 1957).

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CHAPTER 3

KINETIC HORMONES

I. CONTROL OF MUSCLES AND PIGMENTARY EFFECTORS

THE TERM "kinetic" (§ 1.51) brings together a large group of hormones, which act upon certain effectors in the organism in ways which often resemble the effects of nerve stimulation. Kinetic hormones acting upon muscles and pigmentary effectors are considered in this chapter, and those causing the secretion of glands, both exocrine and endocrine, in the next (§§ 4.1 and 4.2).

The similarity in action between these kinetic hormones and some nerves is not entirely accidental, since many of the kinetic hormones are neurosecretions from modified nerve cells (§ 2.111), and some are chemically akin to the acetylcholine or noradrenaline secreted by cholinergic and adrenergic nerves respectively. An important difference lies in their means of distribution; the hormone reaches the effector through the blood circulation and is therefore widespread in its effect, whereas the nerve cell releases its chemical in contact with a single effector only.

There are, however, other kinetic hormones that are not derived directly from nervous tissue. Some of these, like those from the corpus allatum of insects or the adenohypophysis of vertebrates, are likewise derived from the ectoderm. A few others, such as secretin, appear to be derived from neither nerve cells nor ectoderm, but from the endoderm (§ 2.22). The kinetic hormones therefore form a wider group than either "neurohormones" (Welsh, 1955) or the secretions of "neurohaemal organs" (Carlisle and Knowles, 1953); yet they show quite sufficient functional similarity among themselves to warrant their inclusion in one group.

The means of stimulating their secretion may be mechanical, as in the case of gastrin, or chemical, as in that of secretin (§ 4.111); but it is usually nervous (§ 4.32). Few are under the control of any other hormones, and this is probably a question of speed. Hormone action is slower than nerve action; and, whereas the delay due to one hormone may not be significant for the effectors in question, a chain of two hormones might well be so.

The hormones dealt with in the following sections are shown in a series of tables, where they are arranged according to their actions. The hormones of vertebrates have names which are widely accepted and are known to occur in a variety of animals; the example quoted is usually the one described in the text, but in no way implies that the hormone is limited to the genus named. Hormones of invertebrates for the most part have no names and can therefore only be referred to by the organ from which they are secreted. If they have a name, or an abbreviation that is used in the text, this is given in a separate column. Each invertebrate example in the tables is also referred to in the text; it is often the only example from which the hormone has so far been identified.

3.1 CONTROL OF MUSCLES

Muscles can be grouped according to their functions or their histology, and there is some evidence that all types can be influenced by hormones. It will be convenient to take the involuntary muscles of the viscera and heart first, because these are the most commonly subject to hormone control and react similarly, although most visceral muscle of vertebrates is smooth, or unstriated, and that of arthropods and of the hearts in both phyla is striated.

3.11 VISCERAL MUSCLE

In nearly all cases the action of hormones is to stimulate both the rate and amplitude of the contraction of visceral muscle; only rarely is a hormone known to inhibit muscle action (Table 7).

3.111 *Heart muscle*

CRUSTACEA. Control of heart muscle by a hormone has been shown experimentally in the crab, *Cancer pagurus*, and the lobster, *Homarus vulgaris*. Extracts of the neurosecretory "PERICARDIAL ORGANS" (§ 2.112) added to fluid perfusing isolated hearts,

TABLE 7. KINETIC HORMONES CONTROLLING MUSCLES

EFFECTORS	VERTEBRATE		INVERTEBRATE	
	HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
3.11 VISCERAL MUSCLE				
3.111 *Heart: acceleration*	Adrenaline	*Felis*	Pericardial Organ	*Cancer*
,,	—	—	Sinus Gland	*Paratya*
,,	—	—	Corpus cardiacum	*Periplaneta*
inhibition	—	—	CNS	*Paratya*
3.112 *Gut, stimulation of:*				
peristalsis	Gastrin	*Rattus*	Corpus cardiacum	*Periplaneta*
,,	,,	*Felis*	—	—
sphincters	Adrenaline	*Rana*	—	—
gall bladder	Cholecystokinin	*Rana*	—	—
,,	,,	*Felis*	—	—
inhibition of:				
peristalsis	Adrenaline	,,	—	—
,,	Enterogastrone	,,	—	—
3.113 *Genital duct*	Oxytocin	*Rattus*	—	—
	,,	*Oryctolagus*	—	—
3.114 *Myoepithelial cells*	Oxytocin	*Canis*	—	—
3.115 *Blood-vessels*	Vasopressin (ADH)	*Oryctolagus*	—	—
3.116 *Hair follicles, etc.*	Adrenaline	*Felis*	—	—
3.116 *Radial muscles of iris*	Adrenaline	*Homo*	—	—
3.12 SOMATIC MUSCLE				
Body muscles: stimulation	Oestrogen ?	*Sus*	Epistellar Body	*Eledone*
	Testosterone	*Equus*	Suboesophageal ganglion	*Periplaneta*
inhibition	—	—	Eyestalk	*Cambarus*

increase the amplitude and frequency of the heart beat (Fig. 3-1) This action is believed to be due to an *ortho*-dihydroxytryptamine and is closely similar to the action of adrenaline and noradrenaline, which are chemically not widely dissimilar.

Results on other species are rather contradictory, and different doses are needed at different times of year to get similar results. This may be compared with the effects that adrenaline and noradrenaline have on vertebrates, where contraction *or* relaxation can be obtained, according to conditions in the organs resulting from previous treatment, size of dose, *etc.* (Welsh, 1955).

"It is assumed that the function of the pericardial organs in these Crustacea consists in liberating, through fine neuropile-like terminations of the nerve fibres, some hormone passing with the blood into the heart and producing on it a stimulating effect" (Alexandrowicz and Carlisle, 1953). Blood taken from the pericardial cavity before reaching the heart gave the same reaction as the extracts; but that taken from the leg arteries after leaving the heart did not, presumably because the chemical was destroyed before it reached the legs.

Earlier statements (e.g. Welsh, 1937) that the sinus glands of Crustacea provided a heart-accelerating extract might have been unreliable, because insufficient care was taken to avoid the presence of histamines in the extracts (the same is probably true of extracts of sub-neural glands of ascidians credited with similar activity). A heart-accelerating hormone from SINUS GLAND extracts has, however, now been obtained from the freshwater shrimp, *Paratya*, and also an inhibiting extract from the brain (Hara, 1952). They are thought to be distinct from the chromactivators from the same sources (§ 3.223).

INSECTA. The frequency of beat of the isolated heart of the cockroach, *Periplaneta americana*, perfused with a suitable Ringer solution, can be increased some 50 per cent above normal, and the amplitude of the muscle contraction increased also, if an aqueous extract of one pair of CORPORA CARDIACA (§ 2.111) of the same species is added to each 10 ml of the perfusate (Cameron, 1953). At concentrations one-tenth as strong, the amplitude is still increased, but not the frequency. If the extract is separated by paper chromatography, one spot at a time can be eluted and added

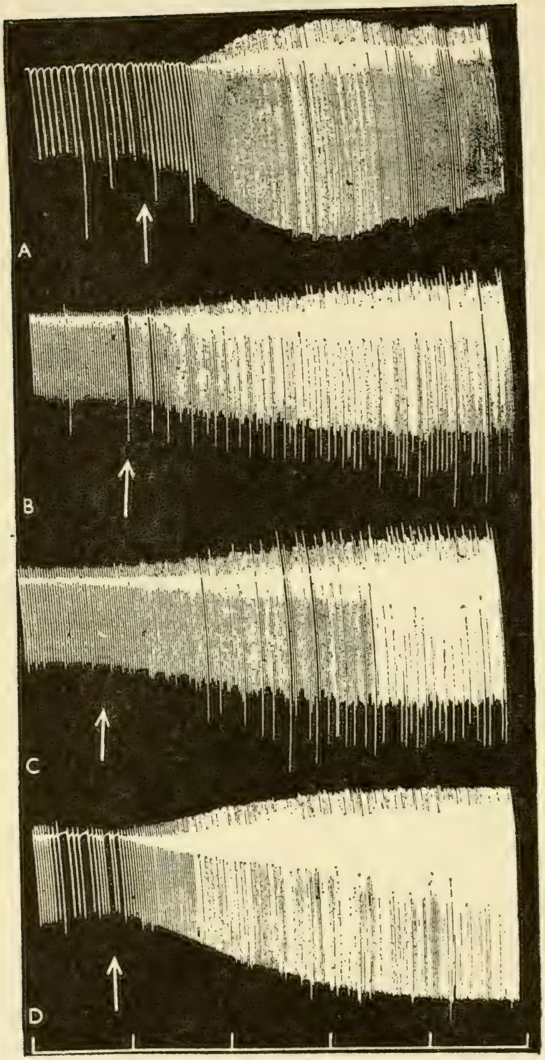

FIG. 3-1. Kymograph record of the heart beat of the crab, *Cancer*. Changes in frequency are shown as abscissae in relation to the time scale in minutes (below); changes in amplitude are shown as ordinates. The record reads from left to right. The arrows indicate the times at which different reagents reach the heart, which is the

to the perfusate. Only one of these shows the same action as the crude extract; this active constituent is thought to be an *ortho*-diphenol (and therefore related to adrenaline). Beautiful as this technique is, it only demonstrates, like most experiments on organ extracts, the pharmacological fact that the animal produces a chemical which has an effect upon the heart. It would be another matter to show conclusively that in life the heart beat is physiologically controlled in any way by this substance, or that in the absence of the corpora cardiaca the animal is unable to control its heart beat to suit the conditions under which it is living. The stimulus which might cause the secretion of the chemical is unknown.

The corpus cardiacum acts as a storage organ for a neurosecretion from the brain, as can be seen in *Leucophaea*, where severing the nerve on one side prevents the passage of the secretion (Fig. 3-2). Yet if a similar operation is performed on *Periplaneta* and separate extracts of the corpora cardiaca of the two sides are tested after 5 and 17 days, that from the severed side is still as active as the other. This eliminates the neurosecretion as a source of the heart-accelerating hormone, which must be the intrinsic secretion of the corpus cardiacum itself. These cells are of ectodermal, rather than nervous, origin (§ 2.112), so that their secretion is one of the few kinetic hormones that is not a vascular "neurohormone" (Welsh, 1955), although its action is akin to that of adrenaline, secreted from cells of the vertebrate sympathetic nervous system (Mendes, 1953).

Adrenaline itself has a similar stimulating effect upon the heartbeat of many invertebrates, whether it is neurogenic or myogenic; but there is as yet no clear evidence of its being secreted by any gland in an invertebrate. In only a few invertebrates is adrenaline used as a chemical transmitter at any nerve ending.

VERTEBRATA. ADRENALINE (§ 2.111) increases the amplitude

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same specimen throughout the series: (*A*) extract of PERICARDIAL ORGAN of *Cancer*; (*B*) adrenaline ($1:10^6$); (*C*) noradrenaline ($1:10^6$); (*D*) the same extract as in (*A*). Between exposures to these substances the heart is restored to seawater and the beat slows down with a reduced amplitude (from Alexandrowicz and Carlisle, 1953).

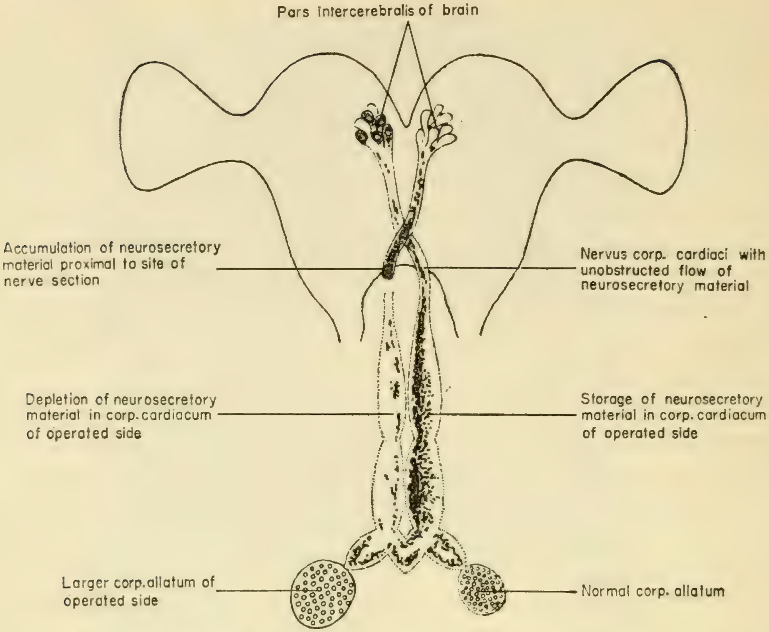
Pars intercerebralis of brain
Accumulation of neurosecretory material proximal to site of nerve section
Nervus corp. cardiaci with unobstructed flow of neurosecretory material
Depletion of neurosecretory material in corp. cardiacum of operated side
Storage of neurosecretory material in corp. cardiacum of operated side
Larger corp. allatum of operated side
Normal corp. allatum

FIG. 3-2. Diagram of the dorsal aspect of the brain, corpora cardiaca, corpora allata and the nerves connecting them in the cockroach, *Leucophaea maderae*. On the left side the nerve from the neurosecretory cells in the brain has been cut, so that the neurosecretion accumulates in the proximal part of the nerve and does not reach the corpus cardiacum of that side (from Scharrer, 1952).

and frequency of the heart beat in Vertebrata. This can only be demonstrated with difficulty in normal mammals, although as little as 1 part of adrenaline in 1,400,000,000 (Turner, 1955) can increase the beat of a denervated heart, freed from the "depressor" action of parasympathetic fibres of the vagus nerve. It is likely, however, that the action of this drug on the heart is usually through the sympathetic nerve, rather than through the circulation, as the drug, or hormone, is quickly destroyed in the tissues by an enzyme.

3.112 *Gut muscle*

INSECTA. The striated muscles in the gut of *Periplaneta* (Cameron, 1953) and *Locusta* will record peristaltic movements for at least

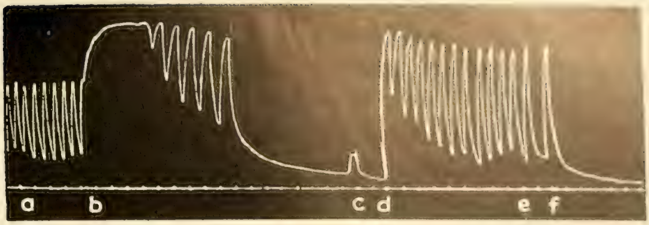

FIG. 3-3. Rhythmic peristaltic contractions of intestinal muscle of the cat, *Felis*; frequency is recorded as abscissae from left to right and amplitude as ordinates. From *a* to *b*, the muscle is in Ringer's solution; then at *b*, and again at *f*, blood from an "excited" cat, that had been barked at by a dog for some time, is added and the contained ADRENALINE causes almost immediate and quite prolonged inhibition of peristalsis. At *d*, peristalsis is restored by changing the perfusing fluid to one containing blood from a "quiet" cat, in which adrenaline secretion had not been stimulated (from Cannon, 1915).

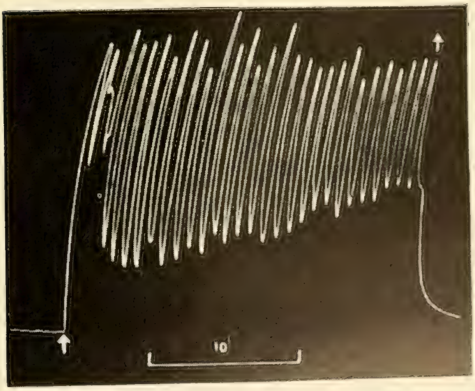

FIG. 3-4. Smooth muscle contraction in isolated rat uterus, showing frequency as abscissae, and amplitude as ordinates. The fresh extract of the neurohypophysis, containing OXYTOCIN, injected at the time indicated by the arrow on the left, induces strong rhythmic contractions. The marked time interval is 10 min. (after Trendelenburg in Buddenbrock, 1950).

24 hours, if perfused with a suitable Ringer solution. In *Periplaneta*, an extract of one pair of its own CORPORA CARDIACA to 10 ml Ringer solution causes the rate of peristalsis in the hind-gut to be doubled, and stronger solutions have more marked effects; but the peristalsis of the fore-gut seems to be inhibited. It is certain, at least in *Periplaneta* and in the locust, that increase in peristalsis of the Malpighian tubules can also be induced by a substance from the corpus cardiacum, as well as possibly one from the BRAIN. The latter observation requires confirmation, in view of Cameron's finding that the neurosecretion from the brain does not contain the active principle causing heart muscle contraction.

VERTEBRATA. The visceral muscle of the vertebrate gut is mainly under the dual control of the nerves of the sympathetic and parasympathetic systems working in opposition; but the effect of the former can also be brought about in emergency by adrenaline from the adrenal medulla.

COLD-BLOODED VERTEBRATES. The effects of ADRENALINE appear to depend upon dosage. In the frog, *Rana*, small doses stimulate the contraction of gut muscles; but larger doses inhibit it (Buddenbrock, 1950).

MAMMALIA. ADRENALINE, secreted in response to excitement or fear, contracts the sphincter muscles of the gut and inhibits peristalsis, as can be shown by adding blood from an excited cat to the Ringer solution in which isolated gut muscle is contracting rhythmically (Fig. 3-3). Both reactions tend to stop digestion and fit in with the emergency mobilization of the blood supply in the somatic muscles.

As its name implies, CHOLECYSTOKININ contracts the muscles of the gall-bladder in frogs and in most mammals. It may also relax the sphincter muscle. The hormone therefore causes discharge of the bile down the cystic duct, and appears to be the only means of stimulating this reaction, for which there is no nerve control (Grossman, 1950). It can be extracted from the duodenal mucosa, and in nature is secreted in response to the presence of fat, or fatty and other acids, in the duodenum. Its histological origin has not been determined, but it appears to be derived from endodermal cells, like secretin, and therefore not to be a neuro-secretory product. It is absent in the horse, *Equus*, which has no gall-bladder.

Gastrin, secreted by the stomach, can induce the contraction of stomach muscles, forcing food into the duodenum as the gastric phase of digestion is completed; but this action of GASTRIN follows, and is subsidiary to, that of stimulating the acid-secreting gland cells of the stomach (§ 4.111). The contraction is said to be inhibited by enterogastrone; but this action is not purely hormonal, since it is more effective if the vagus nerves are intact (Grossman, 1950). The nervous inhibition can be stimulated by acid in the duodenum.

3.113 *Muscles of the genital ducts*

No cases seem to have been recorded so far in which the muscles of any part of the genital ducts of an invertebrate are controlled by hormones.

MAMMALIA. Isolated uterine muscle of many mammals, such as the rat, *Rattus*, reacts to OXYTOCIN from the neurohypophysis by strong rhythmic contraction (Fig. 3-4). At the end of pregnancy these contractions force the embryo out of the uterus. The fact that this does not normally occur until the embryo is fully developed seems to be due, not to a lack of oxytocin during earlier stages of pregnancy but to changes in the level of sensitivity of the uterus. In the rabbit, *Oryctolagus*, the relative insensitivity of the uterus to oxytocin during the 30 days of pregnancy, as compared with variability at other times, is due to the abundant presence of progesterone. As this decreases and oestrogen increases in the circulation towards the end of pregnancy, the uterus becomes increasingly sensitive to the oxytocin until finally it reacts sufficiently strongly to bring about parturition (Fig. 3-5).

Earlier experiments, in which it was found that rats from which the hypophysis had been removed were still able to produce their litters successfully, have now been explained on the grounds that the neurohypophysis is only a storage organ for hormones secreted in the hypothalamus of the brain (§ 2.111), and the experimental technique therefore failed to remove the source of the oxytocin. In those cases where the source was also destroyed by hypothalamic lesions, parturition was not achieved, both the mother and the litter dying in the attempt.

It has also been suggested that oxytocin may play some part in driving sperm upwards into the fallopian tubes after copulation, by affecting the tonus differentially in different parts of the oviduct (Fitzpatrick, 1957).

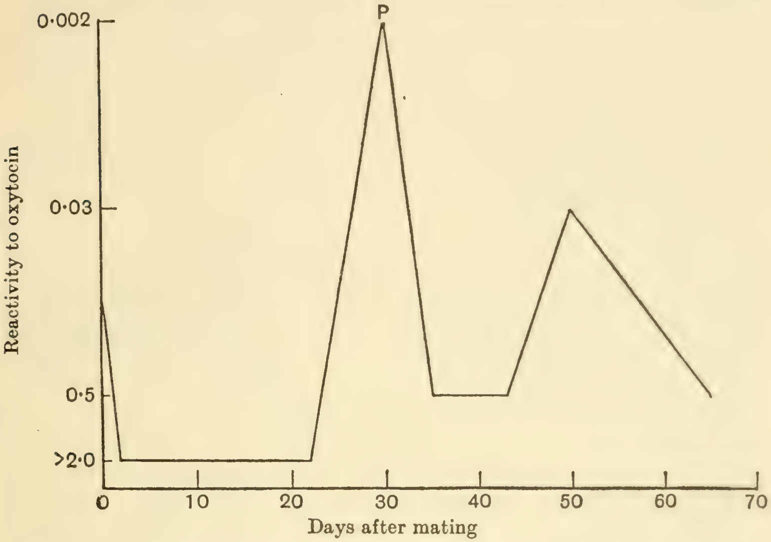

FIG. 3-5. Graph showing schematically the sensitivity to OXYTOCIN of strips of rabbit uterus tested at various stages of pregnancy. Days after mating are shown as abscissae, with the normal term for parturition at P; ordinates (on a logarithmic scale) show reactivity expressed as the minimal number of units of oxytocin which causes a motor effect when added to 100 ml of Ringer-Locke solution (from Robson, 1933).

3.114 *Myoepithelial cells of mammary glands*

There is no known case of a hormone activating the duct muscles or myoepithelial cells of a gland in invertebrates.

MAMMALIA. Branched myoepithelial cells (Fig. 3-6), which surround the alveoli and smaller ducts of the mammary glands, can, by their contraction, drive the milk from the ductules of the gland down into the teats, achieving what is known to farmers as "let-down" of the milk. Figure 3-7 shows that injection of OXYTOCIN into an anaesthetized bitch, *Canis*, stimulates the contraction of these cells, and increases the amount of milk available to the puppies. In the normal state, the act of suckling (or milking) stimulates the brain to induce secretion of oxytocin for this purpose.

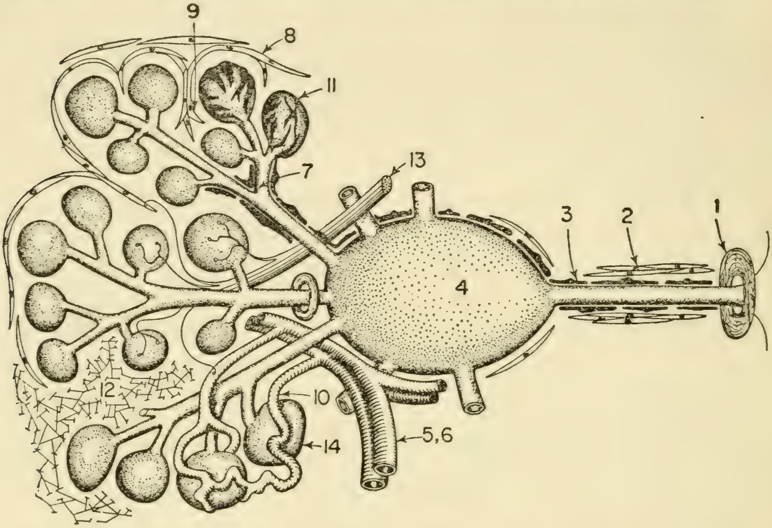

FIG. 3-6. Diagram of a generalized exocrine gland to show the location of factors which may influence the flow of secretion. *Duct activity influenced by:* 1, smooth muscle sphincters; 2, longitudinal smooth muscle shortening ducts or producing peristalsis; 3, myoepithelium; 4, reservoirs in large ducts, or cisterns; 5, vasodilatation pressing on ducts or reservoirs; 6, vasoconstriction shortening inter-lobular vessels and squeezing adjacent ducts; 7, secretion from duct epithelium.
Lobule activity influenced by: 8, smooth muscle bundles in interlobular septa squeezing lobules as a whole; 9, smooth muscle interspersed between alveoli; 10, vasodilatation or vasoconstriction affecting alveoli mechanically; 11, myoepithelium; 12, elastic fibre recoil in stroma, when pressure in distended alveoli is released; 13, nervous stimuli to secretory epithelium and smooth muscle; 14, hormonal stimuli to epithelium. In mammary glands the myoepithelial cells, 11, round the lobules, contract in response to OXYTOCIN. The secretory epithelium, 14, is stimulated by PROLACTIN (§ 4.13). (From Richardson, 1949).

3.115 *Muscles of blood vessels*

No case of hormone control of muscular contraction in the vascular system (vasoconstriction), apart from the contraction of heart muscle, has been reported for any invertebrate except, possibly, in the cephalopoda (p.416).

VERTEBRATA. The arteries of vertebrates react to a number of hormones: for instance, to VASOPRESSIN*, ADH, and to a lesser extent to OXYTOCIN, both from the neurohypophysis (§ 2.114). This effect, which may be merely pharmacological, can best be shown by intravenous injection of vasopressin into any tetrapod after the peripheral blood vessels have been expanded by hypophysectomy (Buddenbrock, 1950).

Certain doses of pure ADRENALINE dilate the peripheral blood vessels when first injected into the rabbit's ear, whereas subsequent injections of similar doses cause contractions (Fig. 3-8). This seems to be unexplained.

3.116 *Other visceral muscles*

VERTEBRATA. Visceral muscles attached to the hair follicles in mammalian skin cause erection of the hair (as on a dog's neck or a cat's tail) in response either to sympathetic nerve stimulation or to ADRENALINE secretion. These also cause the radial muscles of the iris of the eye to contract, thereby greatly enlarging the pupil. The release of adrenaline into the circulation, as a result of fear, shock or rage (cf. secretion in response to excitement, Fig. 3-3), is therefore accompanied by at least the sensation of the hair standing on end, and by the appearance of staring eyes with expanded pupils, and blanching of the face, due to the contraction of the peripheral blood vessels (§ 3.115). More useful features of this "emergency" syndrome due to adrenaline are the increased rate of heart beat (§ 3.111), and the enlarged blood flow bringing a greater supply of sugars to the body muscles (§ 5.211), which enable the animal to achieve a very high output of muscular effort for a time—probably long enough to effect an escape from the predicament causing the original fright.

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* This hormone would be better named antidiuretin from its main action (§ 5.32).

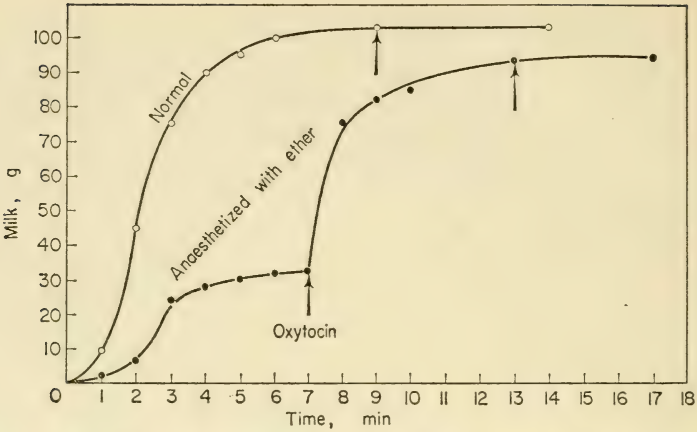

FIG. 3-7. Effect of OXYTOCIN on milk "let-down" in the nursing bitch, *Canis*. The time in minutes is given as abscissae and the amount of the milk yield (as indicated by the increase in weight of the pups) as ordinates. In the normal case, the pups get all the milk that the mammary glands can yield in about 8 min, there being an initial latent period before milk becomes available to them and a falling off as the gland becomes exhausted. In the right-hand curve, starting again at time 0, the pups were put to the anaesthetized mother and failed to obtain more than 30 per cent of the milk, after a very slow start. After 7 min an injection of 0.5 ml Pituitrin containing oxytocin enabled the pups to obtain almost all the rest of the milk, presumably by causing contraction of the myoepithelial cells round the alveoli. The injection of oxytocin has no effect upon the amount of milk secreted, as can be seen by the lack of effect of similar injections made when the curves had already exceeded 90 g (from Gaines, 1915).

In the vertebrates, most types of visceral muscle which are innervated by the sympathetic fibres of the autonomic nervous system are thus seen to react also to secretion from the adrenal medulla; but the nerves of mammals are now known to secrete mostly noradrenaline at their end-plates, whereas the greater part of the gland secretion (derived from neurosecretory cells which originated in sympathetic ganglia) is adrenaline itself, although it is admixed with larger amounts of noradrenaline in the lower vertebrates, e.g. in the secretion of the suprarenal bodies of the elasmobranchs.

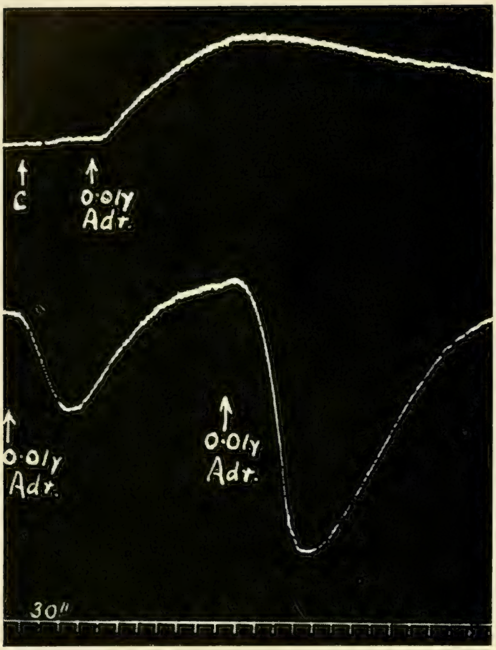

FIG. 3-8. Changes in volume, increasing upwards as ordinates, of the perfused ear of a rabbit, *Oryctolagus*, with time in 30 sec intervals as abscissae. In the upper tracing increase in volume is due to dilation of the blood capillaries following the first injection of adrenaline. The lower tracing shows the opposite effect of two later injections of the same dose. This is an example of reversal from a dilator response of the capillaries to a constrictor response with repeated doses (from Burn and Robinson, in Welsh, 1955).

3.12 SOMATIC MUSCLES

CEPHALOPODA. Ablation of the EPISTELLAR BODY of the octopod, *Eledone moschata* (§ 2.111, Fig. 2-4), is followed by general loss of muscle tone, with even the tentacles hanging limply; but recovery starts about a week after the operation (Young, 1936). In one case the tone gradually returned to normal during the 186 days for which the animal survived, although there was no trace of regenerated epistellar tissue. No attempt seems to have been made to restore the tone by injecting extracts during the first post-operative week; but control experiments made it clear that the effect cannot have been due to shock, which is an important factor in these very sensitive animals with their highly developed nervous systems. The loss of muscle tone extended to the chromatophores, so that animals without the epistellar body became abnormally pale (cf. § 3.21).

CRUSTACEA. Well-controlled experiments (Roberts, 1944) show that exposure of the crayfish, *Cambarus virilis*, to relatively bright light releases an unidentified EYESTALK HORMONE that reduces locomotion. It is possible that this hormone may act either by raising the stimulation threshold of the skeletal muscles of the legs or by lowering the strength of the nerve impulses from the brain; but it seems more probable that the result is due to an indirect metabolic effect (§ 5.1). The reaction may have adaptive value because the animals normally feed by night and escape from predators by remaining hidden by day.

INSECTA. The normal rhythm of nocturnal activity of the cockroach, *Periplaneta*, is stimulated by a HORMONE, from the SUBOESOPHAGEAL GANGLIA, the secretion of which is controlled through the ocelli. If the illumination is kept constant, or the ocelli are painted over, the rhythm disappears. The action of the hormone has been shown by implants and in parabiotic experiments, in which two cockroaches are so joined that blood can flow from one to the other. If, for instance, a specimen in which the ocelli have been occluded has another specimen, with no legs, joined to its back, then normal diurnal changes in illumination acting upon the upper specimen cause a correlated rhythm of locomotor activity in the lower (Harker, 1956).

VERTEBRATA. There are no specific hormones in vertebrates to control somatic muscles, although these are noticeably affected by the hormones from the gonads and also to some extent by thyroxine and adrenaline. For instance, the loss of TESTOSTERONE in castrated mammals, such as cart-horses, results in lowered spontaneous activity and muscle tone, and is shown by the whole stance of the animals, as compared with a stallion, *Equus*. In females, the presence of oestrogen in the circulation during oestrus (§ 4.234 and Part II, § 4) is accompanied by a great increase in activity, as has been shown by attaching a pedometer to a sow. Similar variations in activity are shown during the 4-day oestrus cycle of rats (Beach, 1948); a loss of 82 per cent in muscular activity can follow ovariectomy. It seems probable that all these effects and those of thyroxine may be the result of metabolic changes caused by changes of hormone balance, rather than of any direct kinetic action of the hormones on the muscle contractions, or even on the tonus.

The action of adrenaline is slightly to prolong the active state of the muscle fibres and to increase the tension accompanying a twitch initiated by the nervous system; it does not itself cause contraction of skeletal muscle as it does in the case of visceral muscle (Goffart and Ritchie, 1952).

3.2 CONTROL OF PIGMENTARY EFFECTORS

Pigmentary effectors of a variety of animals bring about colour changes mainly in two distinct ways: one in which extrinsic muscle fibres change the shape of the colour-containing cells, and the other in which the pigment granules themselves are moved within the confines of a stationary cell. Rarely, the cells change shape and may even move their position. These processes cause so-called physiological colour changes (Tables 8 and 9). "Morphological colour change" (Sumner, 1940, and Dawes, 1941) produces similar effects by slow alteration in the total amount of pigment present, rather than by its redistribution. This reinforces the adaptive physiological changes when the external conditions remain relatively constant for days or weeks. Together they play an important part in providing "protective coloration" for the animal.

TABLE 8. KINETIC HORMONES CONTROLLING PIGMENTARY EFFECTORS

EFFECTORS	VERTEBRATE		INVERTEBRATE	
	HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
3.21 CHROMATOPHORES WITH MUSCLES				
Muscle contraction *i.e.* darkening	—	—	Tyramine*	*Eledone*
Muscle relaxation *i.e.* lightening	—	—	Betaine*	,,
3.22 CELLS WITH MOVABLE PIGMENT GRANULES				
3.221 *Simple epidermal cells:*				
dispersal	—	—	Suboesophageal ganglion	*Carausius*
concentration	—	—	?	,,
3.222 *Stationary distal retinal cells:*				
dispersal in light	—	—	Eyestalk	*Cambarus*
concentration in dark	—	—	?	,,
Retinal cells with contractile fibres:				
contraction in light	—	—	Sinus gland	*Palaemonetes*
			,,	*Uca*
relaxation in dark	—	—	Commissures	*Palaemonetes*
	—	—	?	*Uca*

* (Indirect effects)

3.21 CHROMATOPHORES WITH MUSCLES

CEPHALOPODA. This type of chromatophore occurs only in cephalopods, and forms a convenient link between those muscular structures which have been considered in the previous section, and the chromatophores with movable granules which follow.

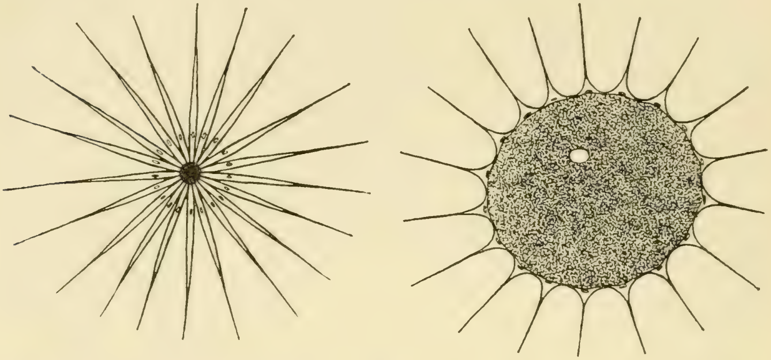

FIG. 3-9. Chromatophores with muscles from a cephalopod, *Loligo*; on the left the muscles are relaxed and the chromatophore cell is elastically contracted so that it looks pale, with the pigment in a small mass at the centre; on the right the muscles have contracted and stretched the cell body to which they are attached so that the chromatophore shows the maximum amount of colour (from Bozler, 1928).

The cephalopod chromatophore (Fig. 3-9) consists of a central pigment-containing cell with a highly elastic wall, and from 4–24 single muscle fibres, attached radially around the circumference; when the fibres all contract, they increase the area of exposed pigment. Contraction of muscles, therefore, corresponds to expansion of the pigment and a darkening in appearance of the animal. Although each muscle fibre is under direct nerve control, the fibres to any one chromatophore usually contract together; but adjacent chromatophores can be separately stimulated to produce the very rapid and varied patterns of colour change which are characteristic of cephalopods and appear to be connected with their emotional states, as well as related to the colour of their environment.

If this were the whole story, cephalopod chromatophores would deserve no place in the present context; but overall changes of colour can also be produced by chemicals in the blood. TYRAMINE from the posterior salivary glands is normally used as poison for paralysing the prey, but is also associated with pigment dispersion, so that animals usually become much darker in colour when the salivary glands are active; BETAINE in the blood is associated with pigment concentration. Moreover, of the three Mediterranean octopuses, *Eledone moschata* and *Octopus macropus* are normally well-coloured species, but *Octopus vulgaris* is pale and habitually has less tyramine in its blood. Transfusion of blood from either of the first two into the last of these species results in darkening. Denervated chromatophores, on the other hand, are completely insensitive to these chemicals (Bacq and Ghiretti, 1951). Tyramine and betaine can therefore be better compared to "para-activators" (§ 1.2) than to true hormones, in that they seem to act through the nervous system and not directly upon the effectors. Their mode of action is still uncertain; Sereni (1930) postulated that they might act directly upon the inhibitory and excitatory centres in the brain, but this has not been fully established.

3.22 PIGMENTARY EFFECTORS WITH MOVABLE PIGMENT GRANULES

Although varying in form and situation, these effectors all contain pigment granules which move to and fro within them, dispersing widely to give a large coloured area, or concentrating into a limited space to give only a small spot. Dispersal here gives the same effect as contraction of the muscles around a cephalopod chromatophore.

The most plausible explanation of how this granule movement is brought about is that given by Marsland (1944) for the branched chromatophores of fish; but it seems probable that the same principle underlies all cases. The pigment granules are attached to a partially gelated system of long protein molecules in the cytoplasm of the cell, and as the cytoplasm gelates fully the molecules contract, drawing the granules "as on a string bobbing through the current" towards the centre of the cell, while squeezing the "plasmosol phase" out into the tips of the cell branches. Dispersal may then be a re-stretching of these proteins on solation, and not a matter of Brownian movement. High pressures (up to 8000 lb/in^2) can be shown to cause solation, and to inhibit the concentration of the granules. This is on a par with amoeboid movement and particularly with muscle contraction; but the problem is still unsolved of whether either nerve stimulation or hormone action can affect the state of the chromatophore proteins in the same way as in the muscles, or whether changes in osmotic pressure (Abramowitz and Abramowitz, 1938) or in permeability of the cell membrane play a part. As a rule chromatophores react much more slowly than muscles; but there is a great difference in the reaction speeds of the similar-looking chromatophores of Amphibia, Reptilia and various Crustacea. This may be a question of the strength of stimulation.

The effectors with movable pigment fall into three types.

(1) The *epidermal cells* of certain Insecta are relatively unspecialized, except for the presence of pigment granules, which may be of more than one colour and may move in different directions (Fig. 3-10, § 3.221).

(2) The *retinal pigment cells* of certain Crustacea and Insecta occur in two positions, proximal and distal, round the ommatidia of the compound eyes (Fig. 3-12, § 3.222), and contain moving granules of black pigment. Movement of reflecting, or white pigment, granules in cells round the retinulae also occurs.

(3) The *branched and specialized chromatophores* of Crustacea and some other invertebrates, as well as of lower Vertebrata, may be epidermal, but are usually mesodermal, and may contain more than one pigment; but if so, each pigment remains in its own branch of the cell (Plate 3-1, § 3.223).

3.221 *Pigment movement in epidermal cells*

INSECTA. The cell-boundaries are reputed to disappear between moults, and the pigment granules can then migrate to an extent comparable with that in chromatophores. In green specimens of the stick insect, *Carausius*, the colour change is obscured by stationary yellow-green pigment; but in brown specimens the red pigment moves parallel to the surface of the epidermis, and the black melanin, which has been more fully observed, moves almost at right angles to it, to cause darkening in appearance (Fig. 3-10). The upward, or dispersing, movement of the melanin depends on both moisture and light, the effects of which are transmitted by the nervous system to the brain, and thence, either by nervous stimulation or by neurosecretion through the circumoesophageal connectives, to the SUBOESOPHAGEAL GANGLION (§ 2.111). This releases a *Carausius*-DARKENING HORMONE which passes in the blood to disperse the melanin. The ganglion cells only release the hormone if the connectives from the brain are intact (Dupont-Raabe, 1956).

If moisture is maintained constant, the melanin granules concentrate in the light and disperse in the dark, and tend to maintain

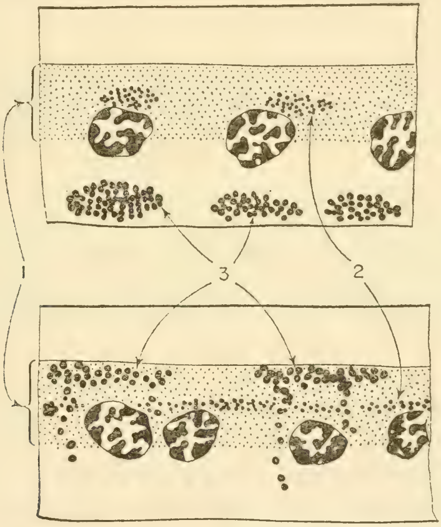

FIG. 3-10. Two diagrammatic sections through the skin of the stick-insect, *Carausius*, to show the movement of pigment granules in epidermal cells. The clear space above indicates the position of the cuticle. The pigment in the upper section is concentrated in the light-adapted position, and in the lower dispersed, in the dark-adapted position. The green pigment (1) remains stationary; the red pigment (2) disperses laterally above the nuclei; the dark, melanin-like pigment (3) disperses mainly outwards (from Giersberg, 1928).

this diurnal rhythm for a time under constant conditions. They show a limited background response, becoming darker on an illuminated dark background than they are on a white or yellow background. In constant light, the melanin disperses in response to moisture, under the control of what is probably the same darkening hormone, since its secretion is also stimulated through the nervous system (Giersberg, 1928). This was established by putting the insect into a humid box, with its head projecting through a diaphragm into the dry air outside (Fig. 3-11); this induces darkening of the whole animal from head to tail in about half an hour. If a ligature is put round the body to prevent the circulation of the blood and hormone to the tail end, the darkening only affects the part in front of the ligature. If the ventral nerve cord is cut at a level just outside the humid box, no darkening takes place, because the stimulus from the damp skin is not conducted to the brain. But if the same animal, with the nerve cord cut but the body unligatured, is then reversed, with its head in the box and the tail left out, the whole body darkens, because the stimulus from the skin of the head can reach the brain, which therefore stimulates the secretion of the hormone. This then circulates freely to all parts of the body. Secretion of the darkening hormone has been located histologically in the suboesophageal ganglia and confirmed experimentally by injection of extracts into animals from which the brain had been removed. Headless animals, lacking the source of the darkening hormone, have their pigment fully concentrated, as in the normal light-adapted animals; they therefore

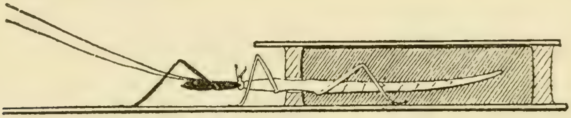

FIG. 3-11. The stick-insect, *Carausius*, with the hinder part of the body in a moist chamber and the head and thorax projecting through a membrane. The pigment dispersion, caused by the moisture, is transmitted by a DARKENING HORMONE from the suboesophageal ganglion. This acts only upon the head and prothorax because of the ligature just behind them (from Giersberg 1928).

form good test subjects for extracts containing the darkening hormone, and show that extracts from other parts of the brain are also active, but those from the corpora allata and cardiaca are inactive (Dupont-Raabe, 1954).

A lightening hormone has not yet been located, partly because of the lack of a suitable preparation for testing extracts. It is not clear why damp-adapted insects with dispersed pigment are not used. One source, at least, of the concentrating hormone must be situated in the body, since it is present in headless animals from which the corpora cardiaca are almost certainly absent (Dupont-Raabe, 1956). Otherwise, it might perhaps have been supposed that the corpora cardiaca would yield a *Carausius*-lightening hormone, since they yield a neurosecretory substance (Cameron, 1953) which concentrates the melanophores of *Crago* (Knowles, Carlisle and Dupont-Raabe, 1955, § 3.223), and some, at least, of the erythrophores of *Leander*. It seems significant that the concentration of both these crustacean chromatophores are light-adaptations, and it is a light-adaptation hormone that appears to be missing from *Carausius*.

3.222 *Pigment movement in retinal cells*

Crustacea. The compound eyes of most Crustacea have three groups of pigment-containing cells round each ommatidium; distal and proximal retinal cells that surround the cone (Fig. 3-12), and reflecting cells that extend below the basement membrane but are not shown in the figure. These last contain white pigment, which behaves like the pigment in white chromatophores (§ 3.223) and is probably under similar hormone control. The proximal retinal cells contain dark pigment granules, which may be fixed in appositional eyes, such as those of *Eupagurus*, but which in many species can be dispersed outwards to isolate the sensitive rhabdomes and convert superpositional eyes into a temporarily appositional type for accurate vision in bright light (Bruin and Crisp, 1957). The movement of the granules in these cells is sometimes a direct effect of light, as in some chromatophores (§ 3.223); but in others it is controlled by hormones, that appear to be the same as those controlling the distal cells (Knowles and Carlisle, 1956).

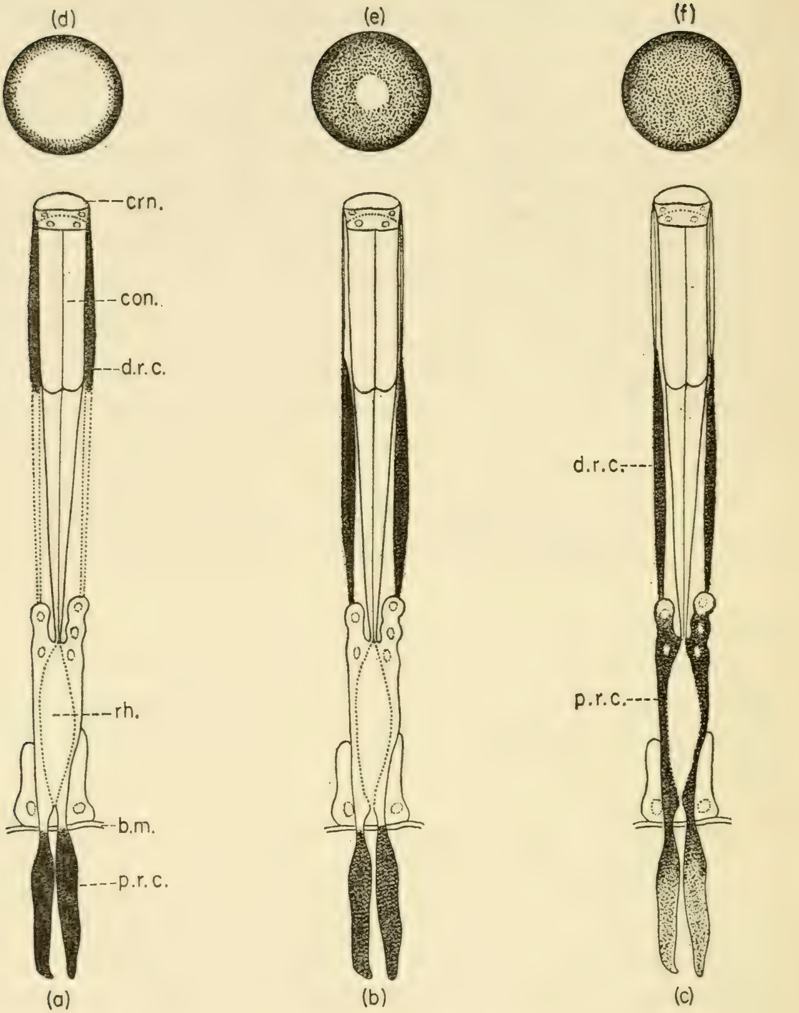

FIG. 3-12. Three ommatidia from the compound eye of the crayfish, *Cambarus bartoni*; *a–c* in longitudinal section and *d–f* in surface view. (*a*) Ommatidium of a typical dark-adapted eye with pigment concentrated at two levels: round the cone (*con.*) in the distal retinal cells (*d.r.c.*), and below the basement membrane (*b.m.*) in the proximal retinal cells (*p.r.c.*). The corresponding surface view (*d*)

The distal retinal cells contain dark, melanin-like pigment granules. The pigment movement can be observed in the intact eye (Fig. 3-12, *d–f*), and is accurately adapted to the light intensity, especially over the lower ranges, such as inshore, underwater animals are most likely to encounter. The adaptive movement is, however, achieved in two different ways: (i) by the usual migration of pigment granules in stationary cells (Fig. 3-12), and (ii) by contractile fibres which change the shape of the cells, thereby causing redistribution of the pigment in relation to the rhabdome (Fig. 3-13). This latter process overrides any sign of pigment migration (Parker, 1932).

Migration of pigment granules in stationary distal retinal cells

In the crayfish *Astacus* and *Cambarus* and the crabs *Dromia* and *Maia*, the pigment granules move inwards to meet the outward movement of the proximal pigment, as they become light-adapted; they move outwards, towards the surface of the eye, to reach the dark-adapted position, which occurs in dim light, rather than in complete darkness. The latter movement appears to be comparable to concentration of pigment in the cell body of a chromatophore; the former inward movement is like dispersal of the pigment into the stationary but outlying cell-processes (Fig. 3-12*c*).

In *Cambarus*, inward migration, or dispersal, of retinal pigments to their light-adapted position is induced by injection of an eyestalk extract, the extent of the migration being dependent on the quantity of the RETINAL-PIGMENT-DISPERSING HORMONE, RPDH, used. The threshold for response of the distal pigment is lower than that for the proximal pigment (Fig. 3-12, *b* and *c*). No

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shows a bright orange centre to the cornea (*crn*), when seen by reflected light, because the rhabdome (*rh*) is unscreened by the proximal pigment. (*b*) and (*e*) In response to the injection into a dark-adapted animal of retinal-pigment-dispersing hormone extracted from one eyestalk, the distal pigment has partially dispersed inwards but the proximal has not moved towards the light-adapted position. (*c*) Extract from two eyestalks has been injected and pigment in both sets of retinal cells has dispersed to the fully light-adapted position. In surface view (*f*) this eye appears black all over, as in a naturally light-adapted animal (from Welsh, 1939).

evidence of the action of a concentrating hormone has been reported (Welsh, 1939).

Movement of pigment due to change in shape of distal retinal cells

Change in cell shape in the prawns *Palaemonetes* and *Leander* and in a Bermudan shrimp *Anchistioides* is brought about by contractile fibres (Welsh, 1936). The distal retinal cells here lie in the same position round the cones of the ommatidia, as in *Cambarus*; but if the usual pigment migration occurs, it is obscured by such a surging inwards or outwards of the protoplasm that even the nucleus is moved as well as the pigment granules, and the whole cell appears to change shape (Fig. 3-13*a*). If the pigment is dissolved away, fibres in these cells can be seen to cause the inward pigment movement by their contraction (Welsh, 1930; Fig. 3-13*b*). It may be noted that physiologically the same effect is produced by this fibre contraction as by pigment dispersal in *Cambarus* (Fig. 3-12*c*), yet these would appear to be opposite reactions in terms of contraction of protein molecules.

Much work on *Palaemonetes* and *Leander* has confirmed the action of a RETINAL-LIGHT-ADAPTING HORMONE, from the SINUS GLAND. This has been found to be similar to that in such Brachyura as *Cancer* and *Uca* (Kleinholz, 1936); but it is not clear if it is the same as RPDH of *Cambarus*. Evidence for an antagonistic, RETINAL-DARK-ADAPTING HORMONE has been found in *Palaemonetes*, and the richest extracts have been obtained from the TRITOCEREBRAL COMMISSURES (§ 2.112; Brown, Hines and Fingerman, 1952).

A persistent diurnal rhythm of movement of distal retinal cells has been shown, at least in continuous darkness, for *Anchistioides* (Welsh, 1936), *Palaemonetes* (Webb and Brown, 1953), and *Leander*, *Praunus* and *Pandalus* (Bruin and Crisp, 1957); for this a hormonal control has been postulated. It is not inhibited by sinus gland removal; but it is probable that the sinus gland is, as in other cases, only the storage organ for the hormone, of which sufficient is still secreted from the source in the ganglionic-X-organ (§ 2.112) to maintain the rhythm.

Changes in distal retinal pigment of grapsoid crabs (R. I. Smith, 1948) are very similar to those in prawns, with a marked

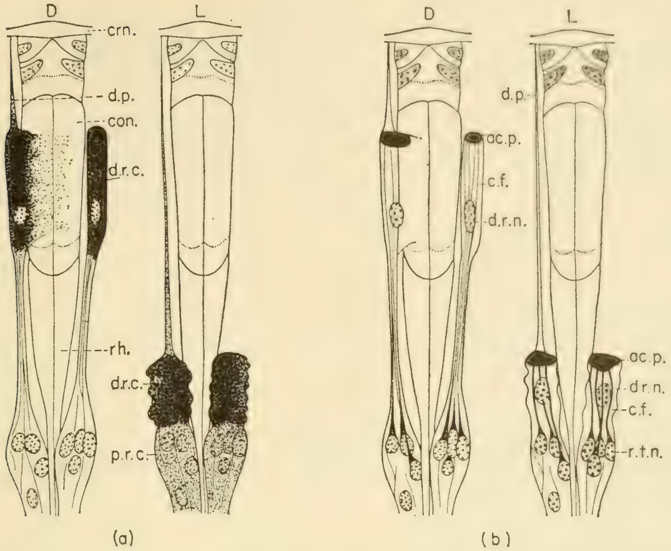

FIG. 3-13. Two ommatidia from the compound eye of the prawn, *Palaemonetes*, in longitudinal section to show pigment cells which change shape. (*a*) In *D*, the ommatidium is shown with the pigment cells in the extreme dark-adapted position; in *L*, in the extreme light-adapted position. As in Fig. 3-12, the pigment in the distal retinal cells (*d.r.c.*) surrounds the cone (*con.*) in the dark position, and the rhabdome (*rh.*) in the light. In *L*, the pigment in the proximal retinal cells (*p.r.c.*, not shown in *D*) has dispersed outwards from below the basement membrane (just out of the figure). (*b*) The same ommatidia with the pigment removed to show contractile fibres (*c.f.*) in the distal retinal cells (*d.r.c.*). They are attached to a mass of accessory pigment (*ac.p.*). In *D*, the fibres are relaxed in the dark-adapted position; in *L*, the fibres are contracted in the light. Most of the cell protoplasm and the nuclei (*d.r.n.*) have moved inwards with the pigment, leaving only an attenuated distal cell process (*d.p.*). The nuclei of the proximal or retinula cells (*r.t.n.*) remain stationary (from Welsh, 1930).

diurnal rhythm that persists in constant darkness; but this is reduced or absent in continuous light. The rhythm can be induced experimentally to become out of phase with the time of solar daylight. About one-third of the dark-adapting hormone of the crab eyestalk is in the sinus gland, and two-thirds in the "optic ganglion", which presumably indicates the ganglionic-X-organ as its source.

The light-adapting hormone for the distal retinal pigment comes from the same source as that which concentrates the red chromatophores of *Palaemonetes* (PLH § 3.223), and the two may be the same, since they both appear to cause contraction of protein molecules. Yet it requires 20 times as much crude extract to be effective on the retinal cells as on the chromatophores (Kleinholz, 1942).

Insecta. The distal retinal cells in the compound eyes of insects can be divided into the same two types as in Crustacea; but the means of controlling their pigment migration is not known.

3.223 *Pigment movement in chromatophores*

There is an embarrassing wealth of detail about the so-called chromatophorotrophic or chromactivating hormones from which it is difficult to select representative examples. They are interesting because they have similar physiological functions in both Crustacea and the cold-blooded vertebrates, and because similar methods of investigation have been applied to both groups, so that they can be directly compared.

Chromatophores are usually elaborately branched cells which apparently remain stationary in the tissues, although they become

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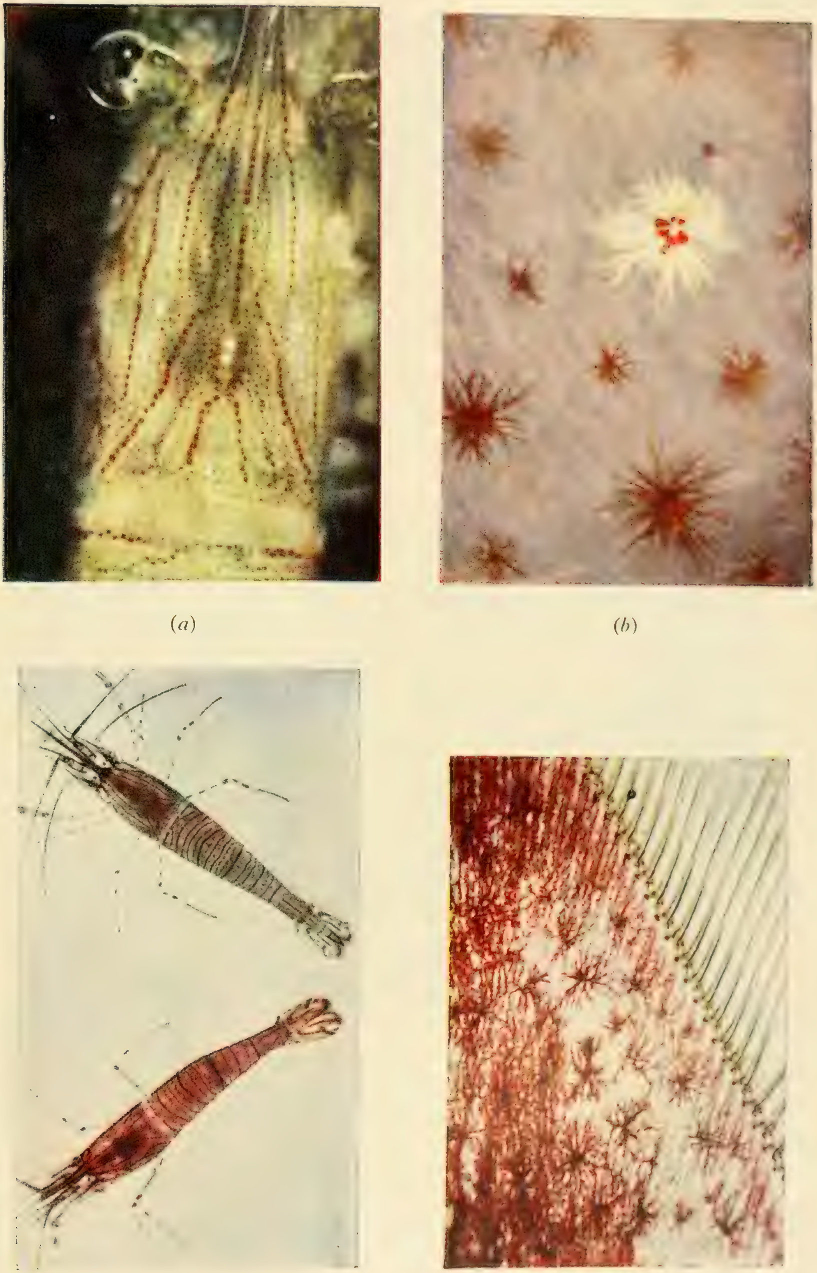
Plate 3/1. Coloured photographs of the prawn, *Leander serratus*. (*a*) Dorsal view of the cephalothorax to show the pattern formed by the differentiation of the chromatophores into large red ones forming the stripes, with small red and white ones between (× 4). (*b*) Part of the same, enlarged to show that there is more than one pigment in each chromatophore; the yellow component in the red chromatophores can be seen faintly and the central red component of the reflecting, white chromatophore is clear. All are fully dispersed (× 50). (*c*) Two eyestalkless specimens kept on a white background, on which red pigment becomes fully dispersed. Half an hour before the photographs were taken each was injected with a different fraction of an extract of the sinus gland. That given to the upper specimen caused strong red pigment concentration; that given to the lower specimen had no effect. (*d*) Part of the tail fan of a specimen like the last, in which the maximum dispersion of red pigment is shown (from Knowles, 1955).

PLATE 3-1



(a)

(b)

(c)

(d)

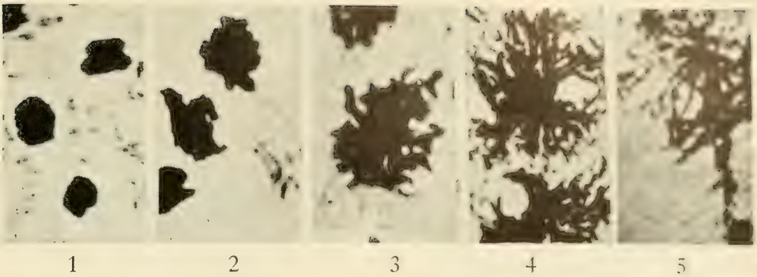


FIG. 3-14. Photomicrographs of melanophores from the web of the foot of the clawed toad, *Xenopus laevis*, with pigment in progressive stages of dispersion corresponding to the melanophore indices 1 to 5. Values such as 1·5 are sometimes recorded directly; but they usually represent the mean of several readings (from Hogben and Slome, 1931)

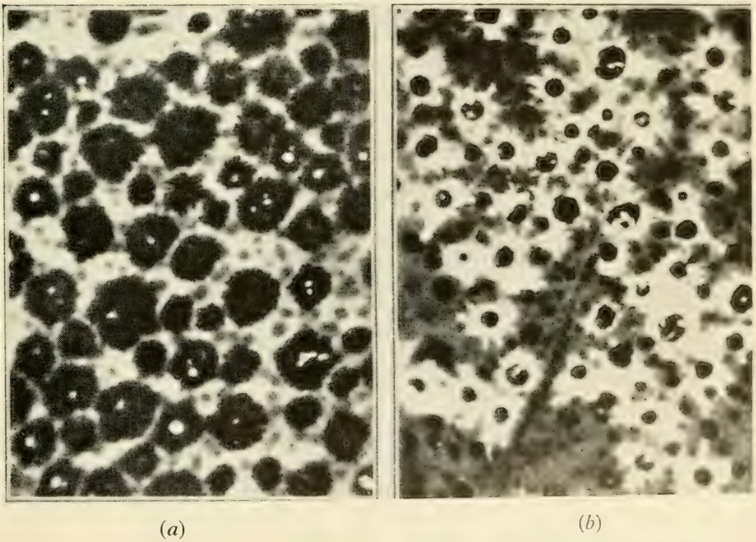


FIG. 3-18. Photomicrographs of chromatophores exposed by removing a scale mid-dorsally from the killifish, *Fundulus*. (*a*) Black-adapted with melanophores dispersed and showing iridosomes at the centre of some; guanophores are concentrated and xanthophores appear grey. (*b*) The same after injection of ADRENALINE. The melanophores are concentrated, and the guanophores widely dispersed as they would be in a light-adapted specimen (from Odiorne, 1933).

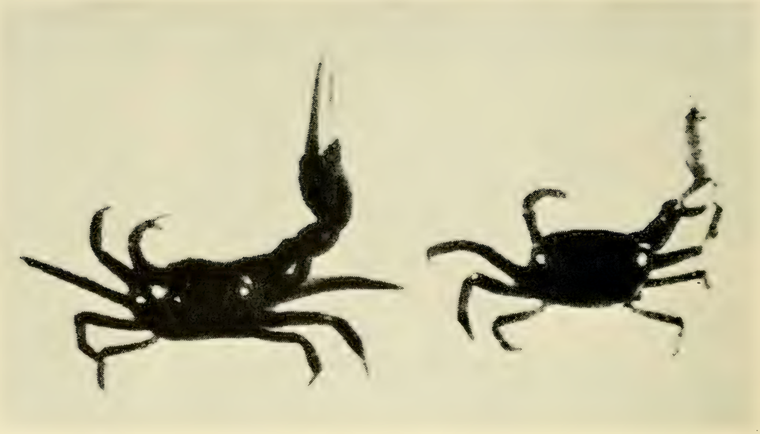


FIG. 3-19. Photographs of the male fiddler crab, *Uca pugilator*, in the light. The normal specimen on the left is dark; that on the right had the eyestalks removed 2 hours previously and the pigment has concentrated in the legs; the pallor shows best in the large asymmetric chela. The carapace is too thick to allow the colour change to be seen through it (from Carlson, 1936).

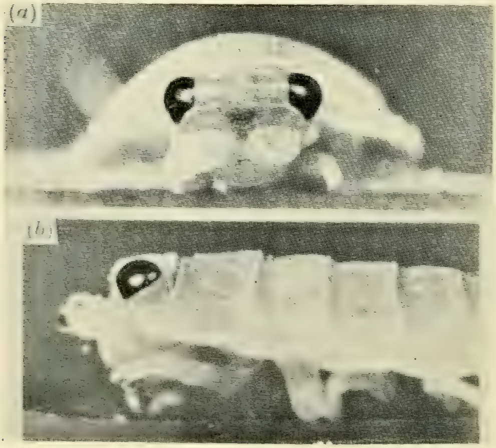


FIG. 3-20. Photographs of the head of the sea-slater, *Ligia oceanica*, with the antennae cut off short. (*a*) Face-view; (*b*) lateral view of the head and eyes, differential illumination of which controls the release of chromactivating hormones (from Smith, 1938).

difficult to see (Plate 3-1) when their pigment granules "concentrate" at the centre. The branches reappear as the pigment "disperses" to their extreme tips. The cause of this pigment migration has already been referred to (§ 3.22).

The cells are sometimes named according to their pigments: "erythrophores" for those with red pigment; "guanophores" with white guanin; "melanophores" with black melanin, and "xanthophores" with yellow pigment. Some cells have black pigments other than melanin. All these colours are to be found in vertebrates; the Crustacea, especially the Malacostraca, have other lipophores, or coloured cells, with a blue pigment as well. Both may have iridosomes, with a movable reflecting material giving a blueish-white appearance (Fig. 3-18).

The control of chromatophores in Crustacea is by hormones only, but can be either by nerves or hormones or a combination of the two in vertebrates. The type of control affects the response somewhat, since hormones, which reach all the chromatophores through the blood, tend to produce a slow and similar response in all parts of the animal, whereas nerve control can quickly stimulate individual chromatophores to produce a colour pattern that may match the background closely, as in Pleuronectidae and chameleons. Such an effect can only be simulated in those Crustacea in which the chromatophores themselves are much differentiated and each type responds to distinct hormones. This seems to be the case in the prawn, *Leander*, in which some chromatophores are large and together form dark bands, while others supply a stippled and variable body colour. They include as least four colours and can be adapted to a variety of backgrounds (Plate 3/1), but their control is not yet fully elucidated (Knowles and Carlisle, 1956), and is too complicated to use as an example here.

Among vertebrates, it is the chromatophores of all Agnatha, Elasmobranchii and Amphibia, but of only some species of Teleostii and Reptilia, that are under hormone control (Fig. 3-24).

The chromatophores of the leeches, Hirudinea, concentrate in light and disperse in the dark, but show no background response. They are probably all under nerve control, and need not be considered here.

A typical background (or albedo) response is related to the amount of light reflected from the background to the eyes. It helps to afford protective coloration to the animal, so that on a light background the result is a pale appearance; but to achieve this the dark pigments must be concentrated and the white dispersed. It is a wide-spread phenomenon in both Crustacea and Vertebrata, and more often than not it is controlled by a pair of antagonistic hormones, which between them can maintain the pigment in the chromatophores at any position between full concentration and full dispersion.

Observation on the behaviour of chromatophores has been facilitated by the introduction of a chromatophore or melanophore index, by which five stages of pigment dispersion are defined, from 1, fully concentrated, to 5, maximally dispersed (Fig. 3-14). Half stages can be used; but it is important to use chromatophores in the same region of the body for successive measurements, as different groups of cells can show considerable differences (Hogben and Slome, 1931). It must also be remembered that intervals on the chromatophore index scale are not quantitatively equal nor exactly related to the dosage of hormone needed to shift the pattern from one stage of dispersion to the next. Their representation by equal intervals on a graph can, therefore, be somewhat misleading.

Before considering hormonal control of responses in more detail, it must be emphasized that several extraneous factors, other than "morphological colour change" (§ 3.2), can also affect chromatophores.

The direct effect of light on chromatophores usually causes dispersion (rarely concentration) in the absence of either nerve connections with a light receptor, or of any hormones in the circulation. Stephenson (1932) showed this clearly in the hermit crab, *Eupagurus prideauxi*, which has functional red and yellow chromatophores, not only on the exposed limbs, but also on the abdomen, where they are usually hidden within the whelk shell that it carries. The direct effect of bright light causes pigment dispersion, whereas the secondary effect, due to hormones stimulated by the eye, is to cause concentration of pigment. On an illuminated light background in a dull light, only this secondary response is elicited, and the animals are pale all over; but in bright light the pigment on the limbs disperses considerably. That this is due to antagonism between the direct dispersion and the secondary hormonal concentration can be seen by quickly removing the crab from its shelter; at first, the newly exposed abdominal chromatophores are concentrated by the hormone effect only, but rapidly darken to match those on the limbs, as a result of exposure to the direct effect of the light. A similar direct effect occurs among reptiles. When a climbing lizard, *Anolis*, is blinded, its chromatophores show dispersal in the light and concentration in darkness (Brown, 1950*a*). The degree of dispersion usually increases with increase in the light intensity.

Temperature increase can concentrate the pigment in the white chromatophores of *Palaemonetes* (Fingerman and Tinkle, 1956) and thereby counteract its dispersion in response to a bright white background. This may help to keep the state of dispersion under control in very bright, hot conditions. In reptiles, such as *Phrynosoma*, concentration of dark pigments at high temperatures may help to prevent excessive heat absorption by the body.

Moisture disperses some pigments, like those of *Carausius* (§ 3.221) and that in the melanophores of the frog, *Rana*, where the concentration due to a light background may be enhanced by dry conditions or almost completely overcome by total immersion. Other degrees of moisture give intermediate results.

A rhythm of colour change related to the tides is said to persist for some time, under still water conditions in the laboratory, in intertidal forms such as the fiddler crab, *Uca pugnax*. A diurnal rhythm of colour change persists under constant conditions of either light or darkness among other Crustacea, Insecta and Amphibia, and may be mediated by hormones in some cases, such as *Uca pugilator*.

In experiments designed to show the action of hormones in controlling physiological colour change, care must be taken to control or eliminate these extraneous factors, affecting the reactions of the chromatophores. Once this has been done, two main lines of attack on the problem can be followed, though a combination of the two is needed for its full elucidation.

The first method is that due to Hogben and Slome (1931 and 1936), who studied the behaviour of the chromatophores in relation to changing environmental factors in intact *Xenopus*. This, which may be called the physiological method, they later extended by the second, or pharmacological, form of investigation, using injections of organ-extracts and purified hormones. The second method has been that chiefly exploited in the search for crustacean hormones by Brown and his co-workers in America; they inject extracts of suspected endocrine organs into variously prepared animals, for which environmental changes are as far as possible ruled out. This method can eventually lead to the location of the source of the hormones, and since about 1942 it has been shown (Brown, 1944), for a steadily increasing variety of pigment cells with moving granules, that two hormones are in control (Table 9), although, for technical reasons, one is usually easier to demonstrate than the other. This, perhaps, accounts in part for the controversy which centred for so long around the problem of whether or not a second antagonistic hormone was necessary to account for crustacean colour change, or whether all the observed changes in any given animal could be accounted for by quantitative differences in a single hormone (Parker, 1948).

The following account of the reactions of chromatophores and their control by hormones in Arthropoda and Vertebrata is only limited to red, white and black pigments in order to simplify the picture (Table 9); this is perhaps to oversimplify it, but it should suffice to give a frame of reference within which to consider further data, such as those relating to the complex system in *Leander* (Carlisle and Knowles, 1959). Much more information is still needed to extend the knowledge of most species from the realm of mere pharmacology towards an understanding of their natural physiology.

Red pigment in chromatophores

CRUSTACEA. Physiological colour change in Crustacea is relatively slow in reaching equilibrium; but it can bring about an almost complete reversal of the state of some chromatophores in two or three hours. For instance, the following observations can be made on the red chromatophores of *Palaemonetes*, or of the fiddler crab, *Uca* (Figs. 3-15 and 3-19), if in the latter case it is remembered that the animals show a diurnal rhythm of colour change in daylight, so that observations must all be made over the same few hours of the day. One group of animals can be adapted

TABLE 9. KINETIC HORMONES CONTROLLING CHROMATOPHORES WITH MOVABLE PIGMENT

EFFECTORS	VERTEBRATE		INVERTEBRATE (ARTHROPODA)		
	HORMONE	EXAMPLE	ORGAN	HORMONE	EXAMPLE
3.223 *Erythrophores* (red)					
Concentrate	Adrenaline	*Phoxinus*	Sinus gland	PLH*	*Palaemonetes*
,,	(Nerve only)	*Holocentrus*	,, ?	ELH	*Eupagurus*
,,	—	—	Commissures	URCH	*Uca*
Disperse	Intermedin	*Phoxinus*	Commissures	PDH	*Palaemonetes*
,,	(Nerve only)	*Holocentrus*	,, ?	EDH	*Eupagurus*
,,	—	—	Sinus gland	URDH	*Uca*
Guanophores (white)					
Concentrate	?	*Fundulus*	Commissures	PWCH	*Palaemonetes*
,,	—	—	— ?	UWCH	*Uca*
Disperse	Adrenaline or "W"*	*Fundulus*	Sinus gland	PWDH	*Palaemonetes*
,,		,,	— ?	UWDH	*Uca*
Melanophores (black)					
Concentrate	"W" (Tuberalis)	*Scyliorhinus*	Sinus gland	CTLH	*Crago*
	,, (Plus nerve)	*Phoxinus*	Brain	CBLH	,,
	,, —	*Xenopus*	Sinus gland	LLH	*Ligia*
	Adrenaline	*Anguilla*	— ?	ULH	*Uca*
Disperse	"B" (Intermedin)	*Lampetra*	Commissures	CDH	*Crago*
	,, ,,	*Scyliorhinus*	,, ?	LDH	*Ligia*
	,, ,,	*Ameiurus*	Sinus gland	UDH	*Uca*
	,, (Plus nerve)	*Phoxinus*	Brain	—	*Chaoborus*
	,, —	*Xenopus*			
	,, —	*Rana*			

* See glossary.

to an illuminated black background, on which the chromatophores will become fully dispersed (index 4.5), and another group to an illuminated white background, on which they will become fully concentrated (index 1). If the backgrounds are then reversed and observations are made on the state of the chromatophores on a chosen part of a leg or chela (the carapace of *Uca* is too thick to allow of satisfactory observation) at short time intervals, graphs of the average values for each group can be plotted to show the gradual dispersion of the chromatophores after the background change from white to black (dotted curve) and the concentration in the reverse case (full curve, Fig. 3-15*a*; Brown, 1950*b*).

The first conclusive evidence that such changes in the chromatophores were controlled by a hormone was obtained by Perkins (1928), who showed for the prawn, *Palaemonetes*, that, although cutting the nerve supply to any part of the body does not interfere with its colour responses to a change of background, a ligature occluding the blood supply to that part stops the response, as in the stick insect *Carausius* (§ 3.221). Release of the ligature restores the response.

Concentration of red pigment in Palaemonetes. The source and action of the red-concentrating hormone that causes the response to a white background has been identified in *Palaemonetes* by the pharmacological method. In the first place it is found that, in prawns and other Decapoda, except the Brachyura, removal of the eyestalks destroys the background response and leads to permanent dispersion of the pigment in the red chromatophores; extracts of the eyestalks can overcome this dispersion and lead to a temporary concentration of the pigment. Within the eyestalk the most potent source of the red-concentrating or *Palaemonetes*-LIGHTENING HORMONE, PLH, is in the sinus gland. Moreover eyestalk extracts from most Decapoda, except crabs, produce this pigment concentration, if injected into a dark, eyestalkless prawn; PLH is therefore not specific to any particular genus (Brown, 1950*a*).

Much contradiction in earlier work was due to the fact that crude eyestalk extracts, containing PLH, were admixed with varying amounts of a second type of hormone that has a darkening effect on crabs. These two kinds of hormones were first separated by fractionation in alcohol (Brown and Scudamore, 1940); but much greater elegance and precision in separating pure substances from the extracts is now possible by paper electrophoresis (Knowles, Carlisle and Dupont-Raabe, 1955). So far the substances eluted

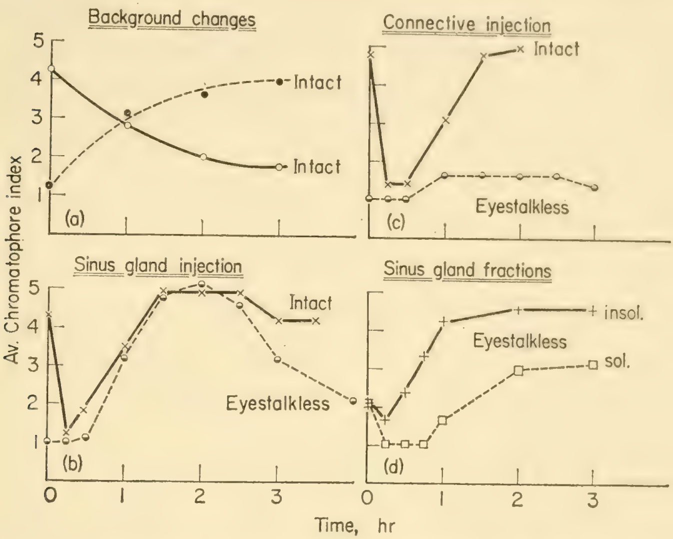


FIG. 3-15. Reactions of the red chromatophores of the fiddler crab, *Uca*. (*a*) The natural background response: the rising curve (dotted line) shows the rate of change of red chromatophores after a light-adapted specimen is transferred from a white to a black background; the falling curve (full line) shows the converse change from black to white, in constant illumination. All measurements were made over the same time of day to avoid the influence of diurnal rhythmic changes. (*b*) The response of intact and eyestalkless specimens from black backgrounds to injections of *Uca*-RED-DISPERSING HORMONE, URDH, from the sinus gland. Prompt dispersal occurs in the eyestalkless specimen; the dark intact specimen shows pallor first, presumably due to operative shock. (*c*) The response of similar specimens to injections of an extract of circumoesophageal connectives. The result indicates a short-lived action of *Uca*-RED-CONCENTRATING HORMONE, URCH, but is ambiguous. (*d*) The responses of eyestalkless specimens to injections of alcohol insoluble (above) and alcohol soluble (below) fractions of a sinus gland extract, to show that the former contains most of the dispersing hormone, URDH (all from Brown, 1950).

from different spots appearing on the paper have only been tested upon eyestalkless prawns kept on a white background; in these the red chromatophores are fully dispersed owing to the lack of PLH, reinforced by the dispersing effect of direct light. It follows that only light-adapting substances causing concentration of red pigment can be satisfactorily identified, though by using sufficiently concentrated extracts relatively rapid reactions can be obtained (Fig. 3-16). Other parts of the nervous system yield extracts with an action similar to that of PLH, but it is more than likely that

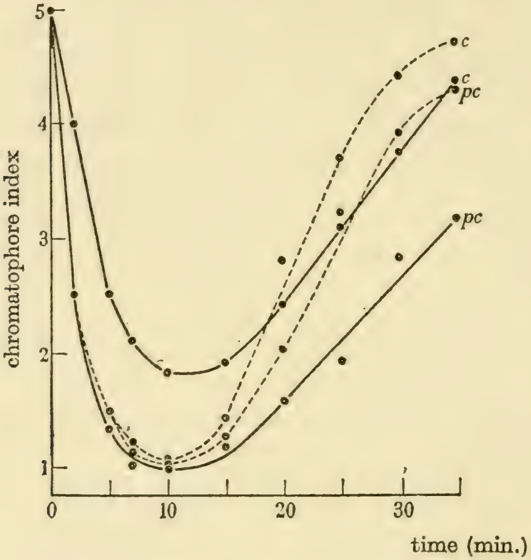


FIG. 3-16. Effect of extracts of the tritocerebral commissures on the dispersed red pigment in the chromatophores of eyestalkless prawns, *Penaeus braziliensis*. The effect of SINUS GLAND extracts would be similar. The abscissae represent time in minutes after the injections; the ordinates, the state of dispersion of the pigment on the same scale as the melanophore index. The dotted lines show that readings taken at night are closely similar to those by day, shown in full lines. The extracts from the post-commissure region (*p.c.*) are rather more active than those from the main commissure (*c.*) in yielding a PIGMENT-CONCENTRATING HORMONE, the effect of which is to cause rapid pigment concentration. This wears off as the hormone is destroyed in the tissues and the pigment returns to its original state of dispersion (from Knowles, 1953).

these are precursor substances, rather than the natural hormone, since they often have mixed effects or need to be "activated" in some way, such as boiling or extraction in alcohol, before becoming effective (Figs. 3-15–17).

Dispersal of red pigment in Palaemonetes. The red-dispersing or *Palaemonetes*-DARKENING-HORMONE, PDH, that acts antagonistically to PLH, has been difficult to locate because it requires a test animal that is pale, yet contains no source of an overriding, concentrating hormone. This has been achieved by starting with eyestalkless specimens of *Palaemonetes* in which the red pigment is fully dispersed (index 5); then at time 0 (Fig. 3-17) an extract containing PLH from either sinus gland or tritocerebral commissures is injected, and pigment concentration becomes almost complete in 15 min (index 2 or even 1.5). After this, the effect wears off slowly as the hormone is destroyed in the tissues and the chromatophores gradually return towards full dispersion. The rate of this return is unaffected by an injection of sea water at 30 min (Fig. 3-17, curve i). If, instead of sea water, an injection of an extract of the darkening hormone, PDH, from either abdominal ganglia or circumoesophageal connectives is given, the rate of dispersion is greatly increased (index 4 is reached in 15 min), and may continue until full dispersion is achieved, within an hour from the start of the experiment (Fig. 3-17, curve ii). This shows conclusively the presence of PDH in the extract, whereas testing this extract on eyestalkless animals which had not been pretreated and were therefore dark, though consistent with this interpretation, does not by itself prove the activity of the extract (Fig. 3-17, curve iii). If PDH is injected into normal, eyed animals with pigment concentrated in the light, only a slight dispersion is produced and this is quickly followed by a return to full concentration, showing that the action of PDH is unable to overcome the naturally secreted PLH (Fig. 3-17, curve iv).

To allow for the natural reversal of the chromatophore response within a relatively short time, a further elaboration of the two-hormone hypothesis has been postulated, namely, that in response to a black-to-white background change, a large amount of PLH is discharged suddenly into the blood, but that "as adaptation becomes complete there would be a reduction of the hormone level to some lower maintenance one". Conversely, a white-to-black change would result in an abrupt discharge of PDH, which would become similarly reduced to some lower level as adaptation became complete. "The introduction of large amounts of either factor, in the presence of a somewhat lower titre of the second,

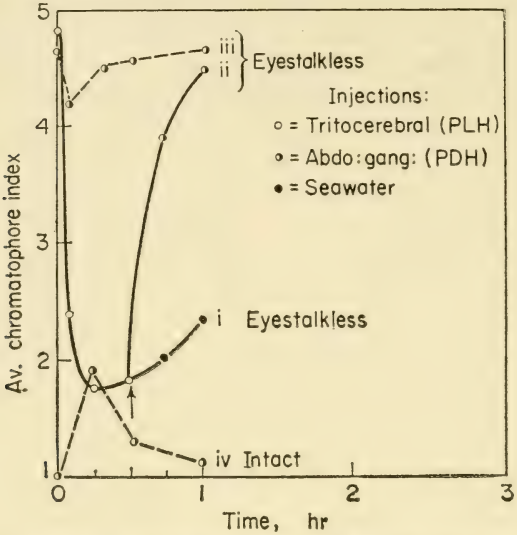


FIG. 3-17. Effects of extracts containing *Palaemonetes*-LIGHTENING and -DARKENING HORMONES, PLH and PDH, on the red chromatophores of the prawn, *Palaemonetes*. Pigment dispersion is shown with time in hours, on a much less extended scale than Fig. 3-16; the extracts are less concentrated and act more slowly. Curves i, ii and iii show effects in eyestalkless specimens with initially dispersed pigment: *curve* i: the effect of PLH injected at time 0 wears off and is unaltered by subsequent injection of seawater at the time marked by the arrow; *curve* ii: PLH injected at time 0 followed by PDH, instead of sea water, injected at the arrow, shows the rapid dispersing effect of PDH; *curve* iii: PDH injected at time 0 produces a slight concentration due to shock and a rapid return to full dispersion. This last is compatible with a dispersing effect of PDH, but does not prove it alone. *Curve* iv shows that injection of PDH only partly overcomes the natural supply of PLH in a normal specimen exposed to light on a white background. PLH was obtained from sinus glands and tritocerebral commissures. PDH was obtained in least contaminated form from the abdominal ganglia (from Brown, Webb and Sandeen, 1952).

effects an initial response which is practically that which would be achieved in the complete absence of the second. Such a mechanism would assure rapid response in either direction, provided the time elapsing between the responses is adequate for the normal reduction in titre after the initial secretory burst"—i.e. about 15–50 min in the black-to-white change, and 30–60 min in white-to-black (Brown, Webb and Sandeen, 1952).

Eupagurus. The red pigment in the hermit crab, *Eupagurus*, (Table 11) behaves like that in *Palaemonetes*; it is concentrated in bright light on a pale background, and dispersed on a dark background. It is clear that both reactions in *Eupagurus* are under hormone control, but the actual substances and their exact sources have not been determined, although removal of the eyestalks again results in persistent darkening.

Uca. The background responses of the red pigment in the chromatophores of the fiddler crab, *Uca*, show well and have already been referred to (Fig. 3-15*a*). Both red-concentrating and -dispersing substances can be extracted from nearly all parts of the nervous system; but, as in most brachyuran crabs, the sinus gland is the richest source of *Uca*-RED-DISPERSING HORMONE, URDH (Fig. 3-15*b* and *d*). As the same is true of the hormone dispersing the melanophores, removal of the eyestalks of crabs results in permanent pallor (Brown, 1950*b*). This is unlike the situation in prawns and most other Malacostraca that have been examined, where the sinus gland provides a concentrating hormone, like PLH, and removal of the eyestalks therefore results in permanent darkening. The main source of the *Uca*-RED-CONCENTRATING HORMONE, URCH, is in the circumoesophageal connectives (Fig. 3-15*c*) and this is again the opposite site from that in the prawns (Tables 9 and 11). The sinus gland also yields small quantities of URCH.

On a constant white background *Uca* also shows a diurnal rhythm of colour changes that are comparable to the direct effects of light and darkness on most dark chromatophores. The crabs become dark by extensive pigment dispersal by day, and pale at night; but these changes in *Uca* are not merely direct effects (p. 84), since their rhythm persists for four days in constant darkness, and it is not altered, although the amplitude of the pigment dispersion is reduced, by reversal of day and night illumination (Webb, Bennett and Brown, 1954).

VERTEBRATA. Relatively little is known of the control of red pigment in vertebrates.

TELEOSTEI. The red (and also the yellow) chromatophores of the minnow, *Phoxinus*, appear to be under purely hormonal control and to show the usual background responses. The dispersing action of INTERMEDIN, B, from the pars intermedia (§ 2.123), is well established (Giersberg, 1930 and 1932), but the source of a red-concentrating hormone has only been rather uncertainly located in the epiphysis or pineal organ. Adrenaline has no effect. Other red pigment cells of fish, such as *Holocentrus*, are controlled by nerves only.

REPTILIA. The erythrophores of the chameleon, *Lophosaura*, are probably under nerve control, like their melanophores, but they do not seem to have been fully investigated (Brown, 1950*a*).

White pigment in chromatophores

CRUSTACEA. The hormonal control of other pigments in chromatophores is essentially similar to that already described for red pigments, though many minor variations have been found (such as those between *Palaemonetes* and *Crago*), and much remains unknown (Tables 10 and 11).

In bright light on a white background the response of guanophores is usually dispersion of their white pigments, which reinforces the pallor produced by the concentration of dark pigments in the other chromatophores. In all the Decapoda examined (except the Brachyura), the richest source of extracts which induce these light-adaptations is the SINUS GLAND, and this is almost certainly the organ where the natural hormones are liberated into the blood; for eyestalk (and therefore sinus gland) removal causes the opposite effect. Like the natural response to an illuminated black background, it results in the white pigment becoming concentrated and the dark pigments being dispersed. Extracts causing the latter effects can usually be obtained from the commissures (which include circumoesophageal connectives and tritocerebral commissures); but it is not known for certain at what point the natural hormone passes into the blood.

Palaemonetes. The white chromatophores (Table 10) reinforce the protective colour change provided by the red pigments of this prawn (Brown, 1950*a*). The concentration of white pigment, which occurs naturally on a dark background, can be induced by injecting an extract from the commissures. This contains a *Palaemonetes*-WHITE-CONCENTRATING HORMONE, PWCH. The dispersion, that occurs on a white background, can be induced by a *Palaemonetes*-WHITE-DISPERSING HORMONE, PWDH, from the sinus glands.

The direct effect of light on the skin is to cause pigment dispersion in these white chromatophores, as it does in erythrophores; but here it reinforces the hormone reaction controlled by the eyes, instead of counteracting it (Tables 10 and 11).

*Crago**. The hormonal control of white chromatophores in the shrimp follows the same pattern as that in *Palaemonetes*. The sources of the two hormones, CWCH and CWDH, are probably similar, but this is not certain. There appears to be no direct effect of light upon the guanophores in the skin, for they remain concentrated, whatever the light intensity.

Uca. In Brachyura, the control of the white chromatophores, like that of the red and black cells of the same animals, follows a pattern distinct from that of the other Decapoda. Although the background response is the same as in the prawns, the source of the *Uca*-WHITE-DISPERSING HORMONE, UWDH, cannot be mainly in the sinus gland, as theirs is, since the pigment remains permanently dispersed in eyestalkless animals. The latter observation suggests that, like the *Uca*-red-dispersing hormone, the source of the *Uca*-WHITE-CONCENTRATING HORMONE, UWCH, might be in the sinus gland; but extracts have not so far given any concentrating effect. There is apparently no direct effect of light upon the white chromatophores of *Uca*, which remain permanently dispersed, even in the dark, in the absence of hormonal control.

TELEOSTEI. The white chromatophores, or guanophores, of the killifish, *Fundulus*, show the same adaptive reaction to background colour as do those of the Crustacea, dispersing on a white background and concentrating on black (Fig. 3-18 *a* and *b*). Their

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* This spelling of *Crangon* is commonly used in this context in America, and is retained here for simplicity.

TABLE 10. CRUSTACEAN HORMONES CONTROLLING WHITE PIGMENT IN RELATION TO LIGHT

ILLUMINATION AND BACKGROUND	ACTION OR SOURCE OF HORMONE	CHROMATOPHORES AND HORMONES		
		Palaemonetes	*Crago*	*Uca*
		NATURAL BACKGROUND RESPONSE		
Bright light on white	Dispersion	* * * *	* * * *	* * * *
	Sinus gland	PWDH†	CWDH ?	—
	Unknown	—	—	UWDH
Bright light on black, or dull light	Concentration	: :	: :	: :
	Commissures	PWCH	—	—
	Unknown	—	CWCH	UWCH‡
		EYESTALKLESS RESPONSE		
Any illumination	—	: :	: :	* * * *
		DIRECT EFFECT		
Bright light	—	* * * *	: :?	* * * *
Dull light	—	: :	: :?	* * * *

* *
* * = dispersed   : : = concentrated.   † See glossary.   ‡ Sinus gland is indicated

normal control may be by nerves, as is that of the melanophores of this fish; but both types of chromatophores react rapidly to injections of either ADRENALINE, or Antuitrin, that supplies a MELANOPHORE-CONCENTRATING HORMONE, MCH (Odiorne, 1933) to give the "light reaction" in which melanophores concentrate, and guanophores disperse (Fig. 3-18*b*). Although denervated melanophores of *Fundulus* are known to disperse in response to injections of B (or MSH), there is only slight evidence that this causes the expected concentration of the guanophores.

Black pigment in chromatophores

CRUSTACEA. The shrimp, *Crago*, is the only member of the Decapoda Natantia so far investigated that has black pigment akin to melanin in cells that may be called melanophores. These melanophores can produce the beginnings of a pattern, because they are differentiated into two sizes, larger on the body and smaller on the tail. These both react to one *Crago*-DARKENING HORMONE, CDH, from the COMMISSURES, but are concentrated independently (Brown, 1946 and 1950*a*); those on the tail by *Crago*-TAIL-LIGHTENING HORMONE, CTLH (alcohol-insoluble extract from the SINUS GLAND), and on the body by *Crago*-BODY-LIGHTENING HORMONE, CBLH (water-soluble extract from the BRAIN), both of which are dominant to CDH. In nature, this means that the shrimp can go wholly dark if only CDH is acting, or the tail or body only may be lightened, while the rest remains dark, according to which of the concentrating hormones are present with the CDH. Finally, if both CTLH and CBLH are present, the shrimp becomes completely pale. An eyestalkless specimen lacks CTLH, and is at first pale with a dark tail, but after a time this effect disappears. The natural stimulation of pattern forming changes in the shrimp is not known; but in prawns, like *Leander*, the extension of a similar system to a large number of different types of chromatophores, apparently each controlled by separate hormones, must give them adaptive advantages by increasing their ability to match a variety of backgrounds (Plate 3-1).

Uca. The background responses of *Uca* melanophores (Fig. 3-19) are more difficult to demonstrate than those of the red chromatophores, because they are almost completely overridden

TABLE 11. CRUSTACEAN HORMONES CONTROLLING RED AND BLACK PIGMENTS IN CHROMATOPHORES IN RELATION TO LIGHT

ILLUMINATION AND BACKGROUND	ACTION OR SOURCE OF HORMONE	RED			BLACK		
		Palaem.	*Eupag.*	*Uca*	*Crago*	*Ligia*	*Uca*
		NATURAL BACKGROUND RESPONSE					
Bright light on white	Concentration	: :	: :	: :	: :	: :	(: :)
	Sinus gland	PLH$^{\alpha}$	ELH ?	(URCH)	CTLH	LLH	—
	Brain	—	—	—	CBLH$^{\alpha}$	—	—
	Unknown	—	—	URCH	—	—	ULH
Bright light on black, or dull light	Dispersion	* * * *	* * * *	* * * *	* * * *	* * * *	* * * *
	Commissures	PDH$^{\alpha}$	—	—	CDH	LDH ?	—
	Unknown	—	EDH	—	—	—	—
	Sinus gland	—	—	URDH	—	—	UDH$^{\beta}$
		EYESTALKLESS RESPONSE					
Any illumination		* * * *	* * * *	: :	* * * * (tail)	—	: :
		DIRECT EFFECT					
Bright light		* * * *	* * * *	* * * *	: : (tail)	(* * * *)	* * * *
Dull light		: :	: :	?	: :	: :	: :

All examples in Table 11 belong to the Malacostraca: *Palaemonetes* and *Crago* to the Decapoda Natantia, *Eupagurus* to the Decapoda Anomura, *Uca* to the Decapoda Brachyura, and *Ligia* to the Isopoda.

: : = concentrated, $\begin{smallmatrix}* *\\ * *\end{smallmatrix}$ = dispersed, $\left(\begin{smallmatrix}* *\\ * *\end{smallmatrix}\right)$ = partially dispersed, in chromatophores.

α = also present in Brachyura: may be A of *Leander* (KNOWLES and CARLISLE, 1956).
β = also present in Macrura: may be B of *Leander* (KNOWLES and CARLISLE, 1956).

by diurnal changes, which operate in the opposite sense. If, however, allowance is made for the diurnal changes, it can just be seen that, for any given intensity of light incident upon the background, the degree of dispersion of the black pigment is greater on a black background than on a white background (Brown and Sandeen, 1948). The *Uca*-DARKENING HORMONE, UDH, controlling dispersion of the melanophore pigment, like the *Uca*-red-dispersing hormone, URDH, is secreted from the sinus gland; eyestalk removal therefore results in relative pallor. The dispersing activity of UDH can be neatly demonstrated by using the two sexes of these crabs (Fingerman and Fitzpatrick, 1956). Melanophores in the female are normally more dispersed than in males in the same situation. If the large, hollow, asymmetrical chela, which distinguishes the male from the female, is removed before the crabs are exposed to light, the operated male becomes as dark as the female. If more legs are removed he becomes even darker. This can best be interpreted by assuming that the same amount of dispersing hormone, UDH, is released in each animal in response to similar stimuli; but that the degree of dispersion of the chromatophores depends upon the concentration of the hormone in the blood. This is increased as the blood volume is decreased by removing successive appendages.

The natural secretion of *Uca*-LIGHTENING HORMONE, ULH, has been demonstrated by using the blood of crabs, in which the melanophores were maximally concentrated, to perfuse isolated limbs on which the melanophores were dispersed. These show slow pigment concentration even if perfused with sea water; but the rate of concentration is increased if perfused with blood containing ULH (Fingerman, 1956). The source of ULH has not been located; but, unlike CTLH, it cannot be in the eyestalk.

Ligia. Apart from the Decapoda so far described, the only crustacean that has had its melanophores investigated in detail is the sea slater, *Ligia*, among the Isopoda. In nature it changes colour from black, when lurking in damp and shady crevices, to pale mottled grey, when exposed to light. On any black background in bright light they show the usual response, by which the melanophores become fully dispersed (index 5). On an experimental white background the pigment can become concentrated to an unnatural pallor (index 1.5, Figs. 3-14 and 3-20). In darkness the melanophores assume an intermediate condition (index 2.7). These reactions are similar to those of the red pigment of *Palaemonetes* (Table 11).

Blinded animals show a direct effect by which the melanophores are more expanded the brighter the light, but never as much as in normal animals on a black background in the same light (Table 12).

If different groups of the ommatidia in the sessile compound eyes of these animals are illuminated separately, either by painting over part of the eye with opaque varnish (which affords a good class demonstration) or by exposing the animals in specially constructed boxes which admit light only to certain narrowly delimited retinal areas (D, L, and V, Figs. 3-20 and 3-21), the effects shown in Table 13 can be obtained.

It is concluded from these and other observations that two antagonistic hormones are involved: a *Ligia*-DARKENING HORMONE, LDH, normally stimulated by direct light on area D to cause dispersion; and a *Ligia*-LIGHTENING HORMONE, LLH, stimulated by reflected light on areas L and V to cause full concentration. When the whole eye is illuminated both are secreted, but LLH overrides LDH to produce almost complete concentration. A balance between the two hormones produces an intermediate effect (Fig. 3-21*b*). The sources of the two hormones have not been fully determined, but Kleinholz (1937) showed that removal of the whole head is followed by dispersion, and extracts of the head cause concentration of the melanophores. The source of

TABLE 12. CHANGES IN MELANOPHORE INDEX IN *LIGIA*

All index values are an average of measurements made on the posterior part of the body of 24 specimens (from H. G. Smith, 1938).

ANIMAL	BACKGROUND	BRIGHT LIGHT	DIM LIGHT	DARKNESS
Normal	Black	5·0 ± 0	4·6 ± 0·08	2·7 ± 0·1
Normal	White	1·7 ± 0·08	1·4 ± 0·06	2·7 ± 0·1
Blinded	White	4·2 ± 0·06	3·9 ± 0·09	2·7 ± 0·1

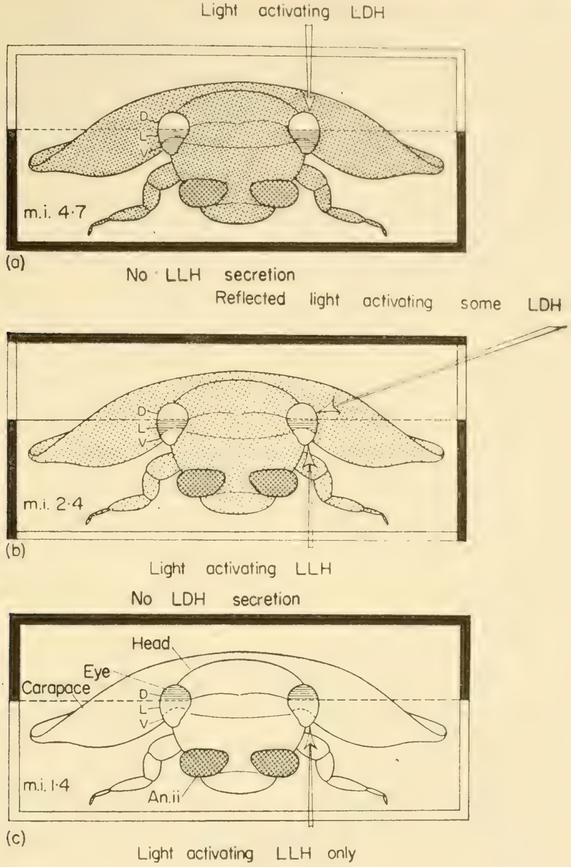
Light activating LDH
D
L
V
m.i. 4·7
(a)
No LLH secretion
Reflected light activating some LDH
D
L
V
m.i. 2·4
(b)
Light activating LLH
No LDH secretion
Head
Eye
Carapace
D
L
V
m.i. 1·4
An.ii
(c)
Light activating LLH only

FIG. 3-21. Diagram of *Ligia*, in face view (cf. Fig. 3-20*a*), to show a method of illuminating separately the dorsal (D), lateral (L) and ventral (V) areas of the compound eyes. Arrows indicate the direction of light falling on the eyes, which are exposed by cutting short the antennae (*An.ii*). The animals are confined in shallow cells allowing horizontal movement only. Screens, indicated by blackened areas, prevent the entry of light. Stippling represents the chromatophore reaction to secretion of LLH, *Ligia*-lightening hormone and LDH, *Ligia*-darkening-hormone. (*a*) Illumination from above only. (*b*) Illumination by direct light from below, with reflected light from above. (*c*) Illumination from below only (Original diagram, based on Smith, 1938).

LLH is therefore probably in the organ equivalent to the sinus gland, since isopods lack eyestalks and the gland lies within the head capsule, in the vicinity of the optic centres, where it is associated with a blood sinus (Hanström, 1939). The source of the darkening hormone is unknown, but must be, in part at least, behind the head.

TABLE 13. ILLUMINATION OF DIFFERENT AREAS OF THE EYES OF *LIGIA*
Blue light is most effective in eliciting these responses in *Ligia*. The index values are averages (from H. G. Smith, 1938).

AREA ILLUMINATED	MELANOPHORE INDEX	CONVERSE AREA COVERED	MELANOPHORE INDEX
D	4·7	L + V	4·6
D + L	2·5	(dark)	2·7
D + V	2·4	—	—
V*	1·8	—	—
V + L*	1·4	D*	1·5
D + L + V (normal)	1·7	none	1·7

* illuminated from below.

INSECTA. The black pigment cells of the phantom midge larva of *Chaoborus* (= *Corethra*) differ from those of *Carausius* in being mesodermal. They normally cover the surface of the two pairs of air sacs and show a background response of the usual protective type; but concentration of pigment on a white background is brought about by an amoeboid change in shape of the cells which become spherical instead of elongated. The cells also tend to aggregate in small groups instead of being evenly spread out to show the maximum amount of colour, as they do on a dark background. Extracts of the brain cause pigment dispersion, and therefore darkening, as in *Carausius* (Dupont-Raabe, 1956).

VERTEBRATA. Melanophore control varies in different fish; among Teleostei it is only in some species that it is wholly under hormone control or even partially under hormones and partially under nerves. Amphibia, where the control is purely hormonal, will be considered first.

AMPHIBIA. The background responses of Amphibia are similar to those of the Crustacea in so far as the animals become pale on an illuminated white background and dark by melanophore dispersion on an illuminated black background. Early investigations of these colour changes were made on the African clawed toad, *Xenopus* and attempted to use the different rates of change of the chromatophores, following changes of background or changes to and from darkness (Hogben and Slome, 1931), to indicate the number of hormones that were necessary to control the changes. The observations were good in that they did not interfere with the integrity of the animals, but recorded their natural physiological reactions. But the changes were so slow and were interfered with by extraneous factors like diurnal rhythms and unsuitable temperatures, so that the results were unsatisfactory. Recourse to the pharmacological method of injecting extracts into variously prepared specimens was therefore necessary to obtain conclusive evidence for the presence of two hormones.

The dispersing or MELANOPHORE-STIMULATING HORMONE, MSH, (known as B to the earlier writers) can be easily established by injection of extracts of the posterior lobe of the frog hypophysis, although the early experiments made use of mammalian extracts. The source is the pars intermedia (§ 2.123).

It has not been possible to prepare active extracts of the antagonistic CONCENTRATING HORMONE, known as W and believed to be secreted from, or controlled by, the PARS TUBERALIS (§ 2.123). The best evidence for its presence is obtained by injecting equivalent extracts of active B substance into variously prepared test toads, and comparing results on a white background (Hogben and Slome, 1936).

Injecting a standard dose of B into the normal pale animal produces a temporary increase in melanophore dispersion that wears off in about 10 hr, when the toad's normal response again takes charge (Fig. 3-22, curve *B*).

If the whole hypophysis is removed, including both the known source of B and the postulated source of W, a much greater effect (Fig. 3-22, curve *A*) is produced for the given dose of B than in the intact animal. The effect also persists longer, just as if the natural supply of W were absent.

If the posterior lobe of the pituitary is removed (taking with it the pars intermedia, which is the source of B, while the pars tuberalis is left intact) a similar dose of B results in the least and shortest response of the three (Fig. 3-22, curve *C*). If there were no active hormone secreted by the pars tuberalis, this curve should be the same as curve *A*, since the source of B is absent in both

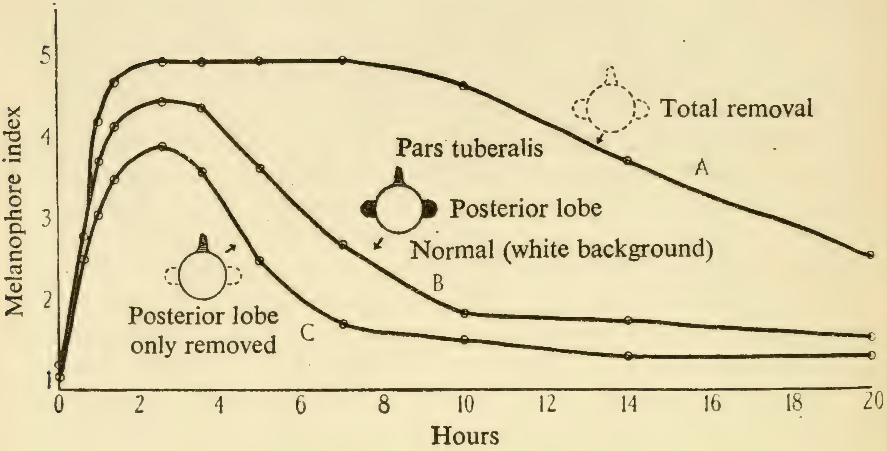

FIG. 3-22. Effects upon the melanophores of *Xenopus* of extracts, containing equal amounts of the melanin dispersing hormone, B (intermedin). (*A*) Six toads from which the whole hypophysis, including sources of both B and W, has been removed. (*B*) Six normal intact toads, in which production of both hormones is stimulated by the white background. (*C*) Six toads from which the posterior lobe and the pars intermedia have been removed, taking with them the source of B only. For further explanation see text. B was obtained from extracts of ox "posterior pituitary", freed from pressor and oxytocic activity, but including intermedin from the pars intermedia to provide a dispersing effect. Although this is not the natural amphibian hormone, the facts of the dose being the same in each case and producing slow dispersion, and the fact that the magnitude of the effect is altered by prior operations on the toads make the results appear significant. The specimens used for the experiments were "selected for the same degree of pallor", and all were exposed to an illuminated white background (from Hogben and Slome, 1936).

cases. The difference may therefore be attributed to the secretion of a large amount of the concentrating hormone, W, by the pars tuberalis in response to the white background (Hogben and Slome, 1936).

The toads always remain pale on a black background after removal of the source of B in the posterior lobe of the hypophysis. If the whole adenohypophysis, including the pars tuberalis, is removed, the toads become permanently dark. That this is due to the loss of the source of W is claimed from finding that, after slightly incomplete hypophysectomy of *Xenopus*, the pars tuberalis may regenerate, in which case the lost response to a white background is regained (Waggener, 1930).

As in *Ligia*, it is claimed that the adaptive colour changes are controlled by the secretion of the two hormones in different proportions in response to illumination of different parts of the retina of the eye by direct and reflected light (Fig. 3-23). The eyes of *Xenopus* are on the dorsal surface of the head and direct light stimulates the "floor" of the retina; on a black background no other light reaches the eye and the secretion of the DISPERSING HORMONE, B, is induced. Scattered light from a white background stimulates the "peripheral" part of the retina and induces secretion of the CONCENTRATING HORMONE, W, whatever position the toad adopts (Hogben and Slome, 1936). In the eel, *Anguilla*, where the eyes are lateral, the ventral and dorsal parts of the retina are assumed to play the same rôle as floor and peripheral parts in the toad.

These results seem to be conclusive; but they lack control injections of saline or of some other non-active substance, and they have not been confirmed by more recent work using better techniques. It is possible, therefore, that there is no real difference between *Xenopus* and the frog, *Rana pipiens*, in which there appears only to be the one melanophore-dispersing hormone, B (Parker and Scatterty, 1937), concentration of melanin resulting merely from absence of B.

ELASMOBRANCHII. The background responses of the melanophores of the rough dogfish, *Scyliorhinus*, and other elasmobranchs are similar to those of the Amphibia, but they seem to be even slower (Waring, 1938). There is no doubt that the melanophores are dispersed by B, since this can be extracted from their own pars intermedia and can also be detected in effective quantities in the blood of dogfish that have been kept on a black background. There is still uncertainty about the presence of the antagonistic, concentrating hormone, W, which is always more difficult to detect. A full review of the literature relating to the chromatophores of these and other fish has been given recently by Pickford and Atz (1957).

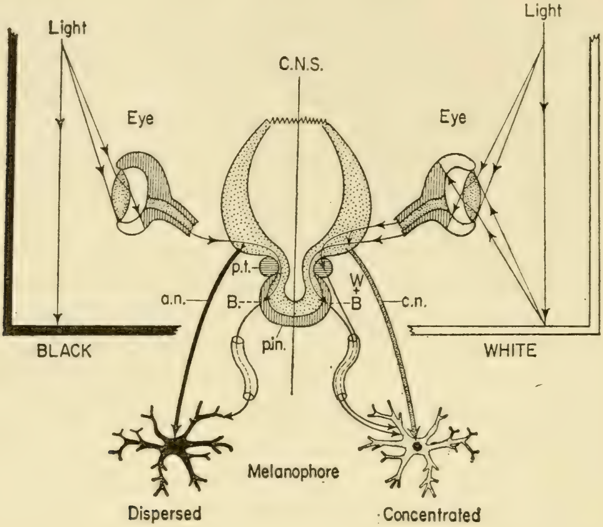

FIG. 3-23. Diagram of the nerves and hormones concerned in mixed control of melanophores in the eel, *Anguilla*. Similar hormones act alone in an amphibian such as *Xenopus*. An illuminated black background is represented on the left and an illuminated white background on the right. On black, only the floor of the retina is stimulated by light and causes pigment dispersion, either by stimulating the secretion of B (MSH) from the pars intermedia (*p.in.*), or by adrenergic nerves (*a.n.*). On white, both the floor and the upper part of the retina are stimulated and pigment is concentrated, either by secretion of B as before and of overriding W (MCH) from the pars tuberalis (*p.t.*), or by cholinergic nerves (*c.n.*). In either case nerves from the eye pass through the brain (*C.N.S.*) to transmit stimuli from the retina to the chromactivating hormone or nerve (from Parker, 1943).

TELEOSTEI. The control of melanophores in the teleosts is more complicated and varied than in the other groups considered, because there appear to be at least two distinct types of response to hormonal stimulation, as well as the differences in reaction introduced by mixed control by both hormones and nerves. In some of the more primitive forms, such as the pike, *Esox*, and the carps, eels and *Ameiurus*, the control appears to be purely hormonal. The melanophores disperse in response to the MELANOPHORE-STIMULATING HORMONE, MSH, from the pars intermedia, when it is injected into pale specimens, whether the source of the hormone is from the same fish, from amphibia or even from mammals. The majority of other teleosts like *Fundulus*, are insensitive to MSH, at least until the melanophores are denervated. This second group is, however, found to be more sensitive to a MELANOPHORE-CONCENTRATING HORMONE, MCH, which is present in most extracts of fish adenohypophyses. It is present in Antuitrin and has no action on Amphibia.

A few teleosts, like *Phoxinus*, although having their melanophores normally under nerve control, can be induced to respond appropriately to both MSH and MCH under suitable conditions. Hormonal control in *Phoxinus* apparently serves to maintain the melanophore reactions over long periods when the nerve control becomes fatigued (Healey, 1948). Many other teleost fish have melanophores which are controlled only by nerves (for further details see Pickford and Atz, 1957).

REPTILIA. Hormones, especially INTERMEDIN, B, play a part in the dispersal of the melanophores of certain of the older genera of lizards, such as *Phrynosoma*, *Hemidactylus* and *Anolis*; but concentration appears to be controlled by ADRENALINE and not by a pituitary secretion. Dual nerve control replaces this in the more highly evolved chameleons and others, producing varied patterns of colour change.

3.224 *Discussion of the hormonal control of pigmentary effectors*

Looking back over the pigmentary effectors just considered (Tables 9, 10, 11), it seems possible to make some generalizations, although the more complex cases have been left out, and the evidence is not always complete for those that have been included. Two hormones are concerned in the control of nearly all types of pigmentary effectors with movable granules, including some which have nerve control as well. But in nearly all cases the actions and sources of one hormone are much more fully established, than those of the other; the more certain of the two is the light-adapting hormone for Crustacea, and the fishes *Phoxinus* and *Fundulus*, whereas it is the dark-adapting hormone for the Amphibia, Elasmobranchii and some Teleostei, such as *Ameiurus*. It seems plausible to expect that in the stick insect, where so far only the *Carausius*-darkening hormone has been found (§ 3.221), an antagonistic pigment-concentrating hormone will be revealed in due course.

In Crustacea there is evidence from Isopoda and from many Decapoda, other than Brachyura, that the hormones producing the light background response are normally stored in, and presumably discharged from, the sinus gland or its equivalent; this is true for the concentration of dark pigments such as black and red, and also for the converse dispersion of the white pigment (Tables 10, 11). Similar converse reactions of the pigment in coloured and white chromatophores in fish may also be due to one and the same hormone, as in *Fundulus*.

The situation in the Brachyura is peculiar. There is a background response, which though slight is similar to that in prawns; but, instead of the concentrating hormone, it is the dispersing hormone which is released from the sinus gland in the eyestalk. In many crabs, such as *Uca*, the background response is overridden by an opposing reaction causing darkening in bright light. It is tempting to interpret this as being either (i) a morphological accident the result of which is that, when light stimulates the sinus gland via the eye, the gland releases its hormone, as in other decapods (but this produces the opposite effect in crabs because the secretion is a dispersing instead of a concentrating hormone); or (ii) the effect of a single hormone controlling dispersion of pigment in both the melanophores and the retinal cells; for dispersion of retinal pigment, as in *Cambarus*, is the adaptive response to light and the daytime dispersion of the crabs' melanophores would then be but following in the wake of their retinal pigment.

It must be emphasized, however, that none of the cases considered (except *Crago*) have more than one colour of pigment in the same chromatophore, unlike the complex pattern-forming chromatophores of *Leander* and *Penaeus* (Knowles, 1955; Knowles, Carlisle and Dupont-Raabe, 1955, and Knowles and Carlisle, 1956), in which there may be as many as four. It is to be hoped that the refined technique developed by these authors for separating pure substances from tissue extracts by paper electrophoresis will soon be extended to the circulating blood of these and other prawns, with their chromatophores in different states of dispersion in response to different states of illumination or background colour. When extracts of tissues yield the same substance as that found to be active in the blood, it should be possible to identify the sources of hormones actually used by the animal, and to distinguish these from other substances, like acetylcholine, produced at nerve endings in the central nervous system; for these can react upon effector systems experimentally, and yet never reach them through the circulation in the living animal (Knowles, 1955).

Modern techniques might also throw light upon the rate of chromatophore reaction, which seems normally to be so much slower in the vertebrates than in the Crustacea, and to be controlled to a considerable extent in the latter by the concentration of the hormone reaching the cells. The rates could be compared with the high speed of reaction of nerve-controlled chromatophores, to see if the differences were due to the more concentrated dose of the chemical which can be supplied at a nerve ending, rather than to differences in sensitivity of the chromatophores (Waring, 1942). Nevertheless, Waring's idea, that an evolution in either the sensitivity of the chromatophore or in its speed of reaction was a necessary precursor of the evolution of nerve control with adaptive value, is interesting. It appears to be borne out to some extent by his table showing that nerve control is only of importance in vertebrates of more recently evolved families, and has not been achieved in the Elasmobranchii and Amphibia, which are both classes with a much longer fossil history than either the Teleostei or the Reptilia (Fig. 3-24). The persistence of purely hormonal control in Crustacea would then be expected, and could be looked upon as having evolved along lines of chromatophore differentiation with multiple hormone control, instead of being replaced by nerve control.

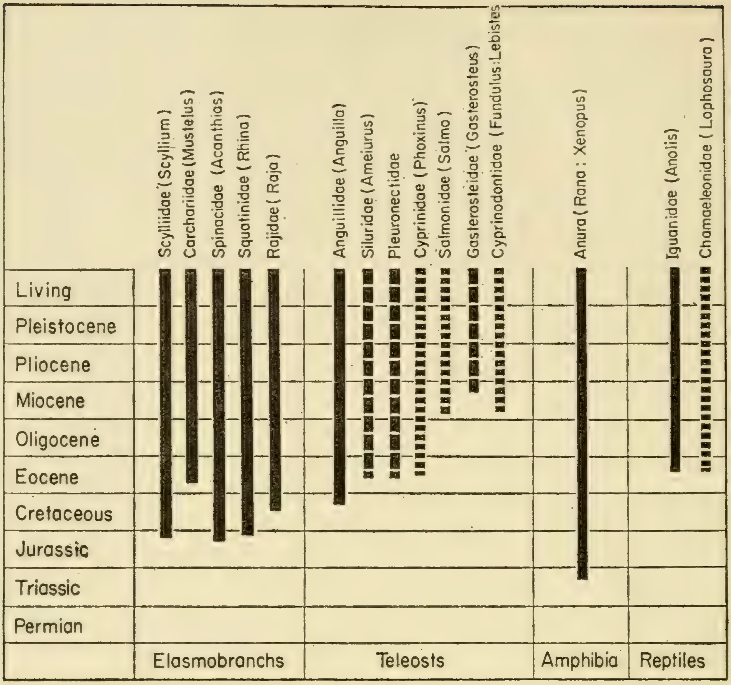

FIG. 3-24. Diagram relating the geological age of certain vertebrate groups to the present day means of controlling their melanophore responses. ▬ predominantly, if not wholly, humoral; ■ ■ ■ ■ mixed humoral and nervous; ▪▪▪▪▪▪ mainly nervous (after Waring, 1942). It seems probable that hormones play a larger part in the control of *Phoxinus* and *Gasterosteus* than this suggests (Healey, 1948; Hogben and Landgrebe, 1940). On the other hand there is some evidence for partial nervous control in some Mustelidae (Brown, 1950*a*).

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CHAPTER 4

KINETIC HORMONES

II. CONTROL OF EXOCRINE AND ENDOCRINE GLANDS

THE HORMONES to be considered in this chapter all act upon glands; most stimulate secretion, though a few inhibit it. They fall into two distinct categories; those that stimulate exocrine glands to secrete to the exterior, or into the lumen of some organ such as the gut or a genital duct (§ 4.1), and those endocrinokinetic hormones that stimulate endocrine glands to secrete their hormones into the blood (§ 4.2). There seems to be every reason for considering the first to be kinetic, like those acting on other effector organs (e.g. the chromactivating hormones, § 3.2), and therefore for classifying the second in the same way (§ 4.2). Yet endocrinokinetic hormones may well be regarded as a group somewhat apart from those acting directly upon other effectors, since their control of bodily functions is not direct but effected through a chain of two hormones.

4.1 EXOCRINE GLANDS

Some exocrine glands secrete continuously; but in many the flow is intermittent, and varied to suit the needs of the organism. The variable glands may, like some of the melanophores, be either under purely nervous control, or purely hormonal control, or even under a combination of the two; but, as far as is yet known, it is only in vertebrates that hormones are concerned. There are, however, some invertebrates where hormonal control of exocrine glands might be expected and others where it has been reported on insufficient evidence.

MOLLUSCA. Intermittent secretion of digestive enzymes is of no advantage to continuous feeders, like the microphagous Lamellibranchia; but it may be of importance in large carnivorous gastropods, such as the whelk, *Buccinum*, or in intermittent browsers like the snail, *Helix*, which do not have food continually in the digestive tract. In the latter, it has long been known (Krijgsman, 1928) that the rhythm of secretion of both the buccal glands and of the digestive diverticula can be accelerated by the presence of food in the mouth and crop; but the mechanism by which secretion is stimulated seems never to have been investigated. It may be nervous; but if not, it may be a direct chemical effect from the food, or it may possibly be due to a hormone, as in vertebrates. Other molluscs in which hormones might be expected are the free swimming cephalopods, such as the squid, *Loligo*. Unlike *Octopus*, which can retire into a crevice and digest its meals at leisure, *Loligo* must complete its digestion rapidly. The successive phases of digestion (Bidder, 1950) and the secretion of a number of enzymes (Romijn, 1935) must be co-ordinated with considerable accuracy. The control may well be nervous in animals with such a well-developed nervous system; but other kinetic hormones exist in *Eledone* (§ 3.12), and might well be sought in the gut of *Loligo* and of the cuttlefish, *Sepia*.

The case of the posterior salivary glands of *Octopus vulgaris* is anomalous, and so far unexplained (Bacq, Fisher and Ghiretti, 1952). The natural saliva yields 5-hydroxytryptamine, which appears to stimulate secretion of these salivary glands; but the secretion produced is abnormal, in being clear instead of viscous, containing no poison, and causing inhibition of the heart instead of stimulation. It seems possible that the salivary extract acts upon the gland by causing constriction of its blood vessels, rather than by stimulating its natural secretion.

ARTHROPODA. The crayfish, *Astacus*, is another invertebrate which secretes digestive enzymes periodically in relation to times of feeding; but the secretion follows a burst of mitotic activity in the gland and is produced by the breakdown of the new cells that result (holocrine secretion; Hirsch and Jacobs, 1930). According to the classification of hormones used in this book, such a process is one of growth that might be controlled by a morphogenetic hormone, but not by a kinetic hormone (cf. submaxillary gland of rat. Part II, § 3). In the beetle *Tenebrio*, it has also been found that a "factor" in the blood is associated with increased mitosis in the mid-gut crypts (Day and Powning, 1949); but there is only presumptive evidence for associating this with increase in enzyme formation, as in *Astacus*.

Cuticle formation in the Arthropoda is due to exocrine glands; but there is little indication of hormones being specifically concerned with their stimulation, although the whole process of moulting is under hormone control (Part II, § 3).

There is as yet no other evidence of hormones in invertebrates controlling the secretion of exocrine glands.

4.11 DIGESTIVE GLANDS

Glands which secrete into the gut occur in all vertebrates; but little is known of the means of their control, except in mammals, where there seems to be a progressive change from the purely nervous control of the salivary glands at the anterior end, possibly through mixed nervous and hormonal control of the stomach glands, to purely hormonal control in the duodenum, pancreas and intestine. In mammals, the action of at least five hormones is to stimulate secretion; but that of enterogastrone seems to be inhibitory, though this is less well established (Table 14). It will be easiest to consider the mammals first, and then to comment briefly on the evidence relating to other classes of vertebrates.

4.111 *Increase in secretion by gut glands*

MAMMALIA. Grossman (1950) has written a comprehensive review of the hormones controlling the secretion of the glands in the mammalian alimentary tract, and has issued a timely warning about the technical difficulties of investigating them. For one thing, the hormones are all secreted by unidentified cells within the mucosa lining the gut (§ 2.21), and not by discrete glands, so that the usual technique of removing the source of the hormone is not available. Moreover, he points out that "the glands of the alimentary tract are capable of responding to, or being inhibited by, a wide variety of substances which cannot be considered to be specific hormones". For instance, when meat is eaten, it yields extracts which are absorbed into the blood and are capable of stimulating gastric secretion. These active extracts are known as "secretagogues"; other tissues contain many other pharmacologically

TABLE 14. KINETIC HORMONES CONTROLLING EXOCRINE GLANDS IN THE GUT

EFFECTORS	VERTEBRATE		INVERTEBRATE	
	HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
4.11 GLANDS IN THE GUT				
4.111 *Increase in secretion*				
Stomach, HCl	Gastrin	Birds? Mammals	—	—
Pancreas, $NaHCO_3$	Secretin	Birds? Mammals	—	—
Pancreas, enzymes	Pancreozymin	,,	—	—
Duodenal glands, enzymes	Duocrinin	,,	—	—
Intestine, enzymes	Enterocrinin	,,	—	—
4.112 *Decrease in secretion*				
Stomach, HCl	Enterogastrone	,,	—	—

active substances, but whether any one of these is a true hormone can only be tested by physiological experiments. Further "it must be remembered that even when an endocrine gland has been identified as producing a hormone, and an active extract has been obtained, no proof has been given in the case of gut hormones, that the extract contains the unaltered physiological hormone".

Hydrochloric acid secretion by stomach glands

MAMMALIA. Although secretin was the earliest of the gut hormones to be identified, gastrin will be taken first, as it is the first to act when food passes down the alimentary tract and reaches the pyloric end of the stomach. A flow of acid from oxyntic cells and pepsin from the gastric glands in the fundus or cardiac region of the stomach is stimulated by the release of GASTRIN into the circulation from cells situated in the mucosa lining the pyloric region of the stomach (Fig. 4-1). Much evidence pointed in this direction before the action of the hormone was conclusively established in 1948 (Grossman *et al.*). Their proof lay in experiments on dogs, and followed a classical pattern. Operations in two stages provided animals with two stomach pouches separated from the rest of the alimentary canal, devoid of nerve supply, and with the original blood supply replaced from the vascular tissue (e.g., mammary gland) into which the pouch is grafted in a subcutaneous position. There the changes in secretion within the pouch can be measured by collection through a fistula to the exterior (at 4, Fig. 4-2). Whether it was the fundus or the pylorus of the stomach which was moved in this way, the results were essentially the same. When a small balloon was inserted into the pyloric pouch and inflated, an increased secretion from the fundus pouch and a marked increase in its acidity followed (Fig. 4-3). Since there was no nerve connection, transmission of stimulus from one part to the other must have been through the circulation. It was observed that the reduction in blood flow, following the severing of the original blood supply to the cutaneous graft, reduced the response. At the same time, the fact that the stimulus to the pyloric region was only mechanical distension ruled out the possibility that the humoral agent carried in the blood was a secretagogue, derived directly or indirectly from the digestion of food in the stomach. This evidence for a hormone, secreted from the pyloric region of the stomach, causing the secretion of acid from the fundus region has also been supported by the use of purified gastrin, extracted from the stomach wall and freed of histamine and secretin. Injection results in an increased flow of acid, but in little change in the pepsin content of the gastric juice.

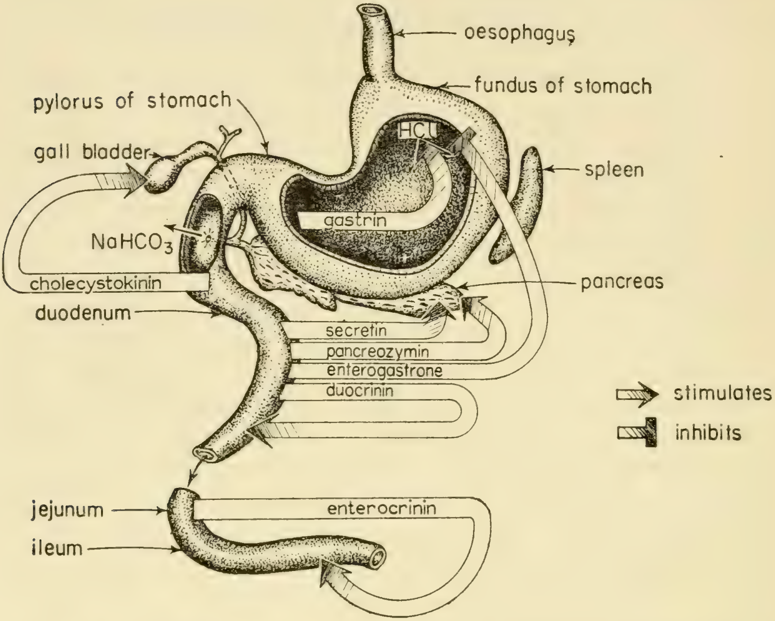
oesophagus
fundus of stomach
pylorus of stomach
gall bladder
HCl
spleen
gastrin
NaHCO3
cholecystokinin
pancreas
duodenum
secretin
pancreozymin
enterogastrone
duocrinin
stimulates
inhibits
jejunum
ileum
enterocrinin

FIG. 4-1. Diagram to show the actions of hormones in the mammalian gut. Heavy arrows extend from the source of each hormone to the effector which it controls, either by stimulation or inhibition. SECRETIN stimulates the secretion of bicarbonate; PANCREOZYMIN, DUOCRININ and ENTEROCRININ the secretion of enzymes. In addition to their effects upon the secretion of HCl, GASTRIN and ENTEROGASTRONE stimulate and inhibit respectively the muscles of the stomach. CHOLECYSTOKININ only stimulates the muscles of the gall bladder and relaxes its sphincter (amplified from Turner, 1955).

The secretion of GASTRIN is therefore stimulated either by food or by mechanical distension; it is secreted from the mucosa of the stomach, chiefly in the pyloric region, and stimulates the exocrine glands of the mucosa in the fundus to secrete HCl into the lumen of the stomach. There is some evidence that as acid increases in the stomach the secretion of gastrin is inhibited. Nerves of the vagus can also stimulate the flow of gastric secretion; but it seems clear from experiments like the above that they are not necessary for the release of either gastrin or of acid. How far they may increase the natural secretion of the juices and their enzyme content is not clear.

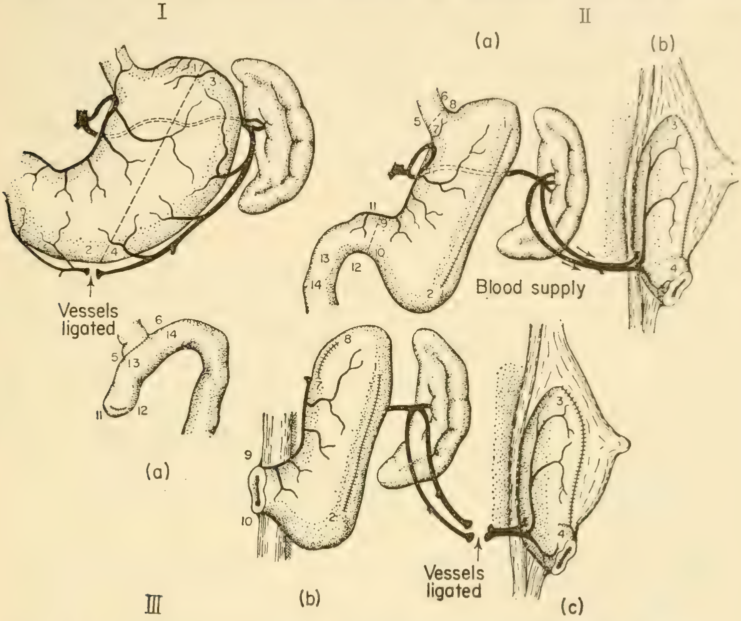

Fig. 4-2. Diagrams showing the two operative stages by which a pouch from the fundus of the stomach of a dog, *Canis*, is isolated from the rest of the gut and grafted into the mammary gland, where it acquires a new blood supply (I, II*b* and III*c*), and an opening to the exterior at **4**. The remaining pyloric part of the stomach is stitched up and later brought to the exterior by an opening at **9**, **10**. (I, II*a* and III*b*). The oesophagus at **5**, **6** is joined to the duodenum at **13**, **14**, so that food by-passes the stomach (II*a* and III*a*). This arrangement was used to demonstrate the presence and action of gastrin (from Grossman, Robertson and Ivy, 1948).

COLD-BLOODED VERTEBRATA. There is as yet no certain evidence of the natural action of gastrin in any class of cold-blooded vertebrates. Frogs have been found to respond to injection of mammalian GASTRIN by an increased gastric secretion; however, the natural physiological stimulus seems to be brought about by the sympathetic nerves. In Elasmobranchs, on the other hand, it has been claimed that both adrenaline and sympathetic stimulation serve only to inhibit the flow of the gastric secretion, while histamine or acetylcholine, but not vagal stimulation, increases it (Prosser, 1950). This rather contradictory state of affairs clearly merits further investigation.

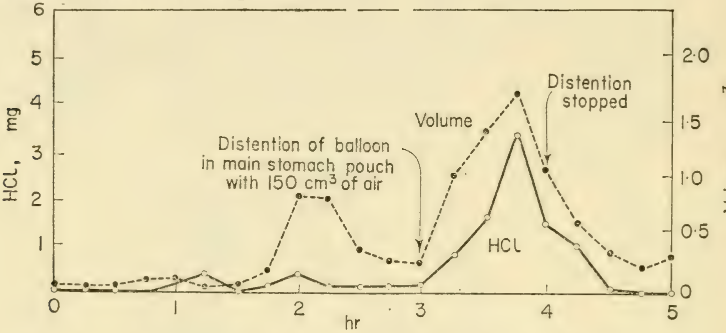

FIG. 4-3. Result of an experiment on a dog, with two isolated stomach pouches, as in Fig. 4-2. Time in hours is plotted as abscissae, and output of acid from the fundic pouch as ordinates; the output is stimulated by gastrin, and is shown by weight of HCl (below) and by the changes in volume of the pouch (above). The acid increases markedly in response to the mechanical stimulus of a balloon inserted into the pyloric pouch and inflated with air at the point indicated. When distention in the pyloric pouch stops, the secretion in the fundic pouch falls off rapidly with the fall in GASTRIN production (from Grossman, Robertson and Ivy, 1948).

AVES. Birds are among the few forms, other than mammals, in which positive evidence has been found for injected GASTRIN stimulating the acid gastric secretion in the proventriculus (Keeton *et al.*, 1920). Its physiological action has not been shown.

Bicarbonate secretion by the pancreas

MAMMALIA. SECRETIN was discovered in 1902 by Bayliss and Starling; but it was many years before its action was fully proved.

It is produced from the duodenal mucosa by the action of the acid chyme entering from the stomach. Pavlov (1910) and others showed that this stage in digestion initiates a copious flow of secretion from the pancreas into the duodenum, and that this still occurs after section of both the vagus and sympathetic nerve

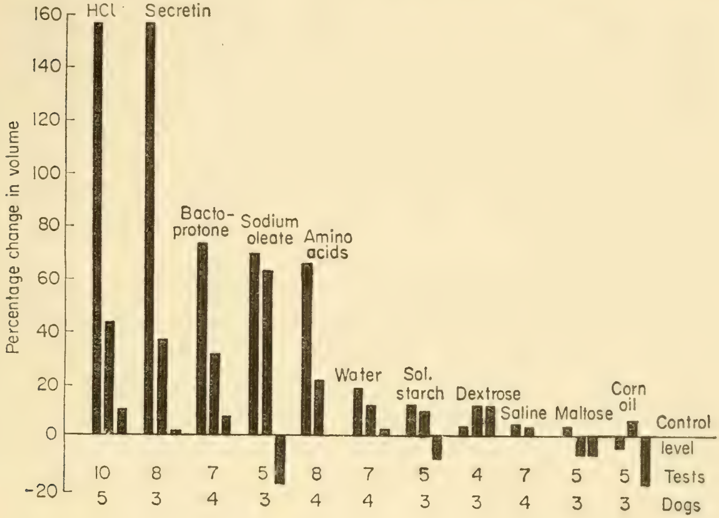

FIG. 4-4. Diagram showing the effectiveness of various substances introduced into the lumen of the duodenum in inducing secretion of bicarbonate from a transplanted pancreas. The collected pancreatic secretion indicates by its change in volume (ordinates) the quantity of SECRETIN released into the circulation from the duodenum. Under each substance three vertical bars represent three consecutive 20 min collecting periods; each result is the mean of 4-10 tests, carried out on 3-5 dogs in each case. Acid and secretin are equally effective; peptones and amino acids much less so (from Wang and Grossman, 1951).

supply; a completely denervated loop of the intestine of a dog, if treated with acid in the lumen, can start the pancreatic flow, so long as the circulation is intact. The stimulus for pancreatic secretion is shown, by this and other cross circulation and transplantation experiments, to be due to a blood-borne factor, and not to be dependent upon any nerve reflex between the gut surface and either the cells secreting the factor or the pancreas. Direct introduction of acid into the circulation is not effective in causing the pancreatic secretion; whereas introduction of extracts of the duodenal mucosa brings on the flow of secretion within about one minute.

Small quantities of secretin can also be extracted from the gastric mucosa; but the main source is from the duodenum, and consequently its secretion is only brought about by placing acid in this part of the gut. Acid in the stomach or the lower part of the intestine has no effect in stimulating pancreatic secretion. The natural acid is hydrochloric from the stomach; but any buffer that keeps the duodenal contents between pH 4 and 5 stimulates the production of secretin (Grossman, 1950). Peptones and amino acids are much less effective (Fig. 4-4).

The pancreatic glands which are stimulated by SECRETIN produce an alkaline solution containing $NaHCO_3$; as this secretion brings the duodenal contents to neutrality, the stimulation of secretin stops and the flow of alkali from the pancreas also stops, the end point of this hormone-controlled titration having been reached. Secretin also increases the flow of bile from the liver; but enzyme secretion from the pancreas is stimulated by the vagus nerve or by pancreozymin (Table 14).

COLD-BLOODED VERTEBRATA. Elasmobranchs, salmon, frogs, salamanders and some reptiles, such as tortoises, have all been found to yield extracts, which act like secretin in mammals; but it is not certain that all the extracts contain the same chemical as the mammalian hormone: they may owe their activity to the presence of histamine, which is a potent secretagogue for the pancreatic glands. There is no evidence for the hormone having any natural function in these animals.

AVES. Claims made for the presence of secretin in birds appear to be founded on some confusion between this hormone and gastrin. They are said, however, to respond to injection of SECRETIN.

Digestive enzyme secretion by the pancreas

MAMMALIA. PANCREOZYMIN, like secretin, is secreted from the mammalian duodenal mucosa and acts upon the pancreas (Fig.

4-1); but, as its name implies, it stimulates those gland cells which secrete the digestive enzymes. Vagal stimulation also facilitates the secretion of enzymes; but the action of the hormone persists after bilateral section of both the vagus and the sympathetic nerves. Experiments (Wang and Grossman, 1951) on transplanting the pancreas, to eliminate any possibility of nerve connection between the duodenum and the pancreas, prove the presence and independent action of pancreozymin as a hormone.

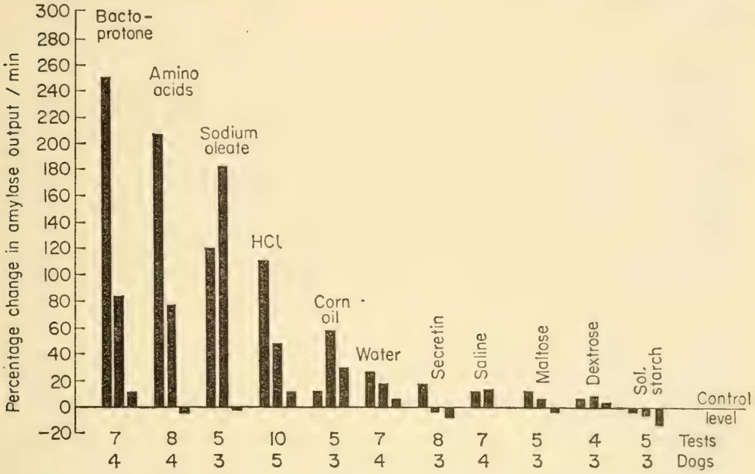

FIG. 4-5. Diagram, as in Fig. 4-4, showing the effectiveness of various substances in stimulating enzyme secretion from a transplanted pancreas, for 3-5 dogs in each case. The change in enzyme secretion indicates the quantity of PANCREOZYMIN released into the circulation from the duodenum, in response to each substance. Peptones and amino acids are more effective than acid in stimulating pancreozymin secretion (from Wang and Grossman, 1951)

The stimuli that have been reported to cause the release of pancreozymin include soap, peptone, casein, starch, various sugars and even distilled water, introduced into the duodenum; they have now been rigorously tested on pancreatic transplants. These experiments show that peptones and the amines, leucine, tryptophane and phenylalanine, resulting from protein digestion, are more effective than acid (Fig. 4-5).

Digestive enzyme secretion by the duodenum

MAMMALIA. There is some evidence (Grossman, 1950) for DUOCRININ being secreted like secretin, from the mucosa of the duodenum in response to acid, but it acts upon Brunner's glands in the wall of the duodenum itself and not upon the pancreas. It appears with secretin in crude extracts of the mucosa, but is separable from it.

Digestive enzyme secretion by the intestine

MAMMALIA. Certain peptones in contact with the intestinal wall stimulate the secretion of ENTEROCRININ, which increases the succus entericus, both in volume and in enzyme content. The gland cells that secrete the succus entericus are in the walls of the jejunum and ileum. The cells that secrete enterocrinin are confined to the same region of the intestine, but have not been identified histologically.

4.112 *Decrease in secretion by gut glands*

A number of hormones have been postulated as having an inhibiting effect upon the exocrine glands of the mammalian gut; but such an action is difficult to prove because so many factors in the experimental procedures are liable to reduce either the activity of the gland or the sensitivity of the tissues at one point or another in the chain between the gut surface, the endocrine cells and the exocrine glands.

Inhibition of acid secretion by stomach glands

MAMMALIA. The most clearly established of the inhibiting hormones is ENTEROGASTRONE. Its source, like that of some stimulating hormones, is in the duodenal mucosa; but its action is to counteract that of gastrin and to inhibit the secretion of acid by the gastric glands, thereby bringing to an end the gastric phase of digestion and facilitating the neutralization of the gut contents as they pass into the duodenum (Fig. 4-1).

"Among the agents which inhibit gastric secretion when present in the duodenum, fat is the only one which has been proven by experiments with the transplanted pouch to act by release of enterogastrone. Concentrated sugar solutions, which have been shown to be capable of inhibiting gastric secretion when present in the duodenum", probably act in the same way. "Curiously, although gastric motor inhibition by acid in the duodenum depends on the integrity of the vagi, the gastric secretory inhibition apparently does not. This phenomenon deserves further study" (Grossman, 1950).

To summarize the situation in mammals: when food distends the stomach, GASTRIN causes the secretion of acid in which digestion starts. As this acid passes on into the duodenum, aided by gastrin stimulating the stomach muscles to contract, it causes SECRETIN to stimulate the flow of neutralizing alkali from the pancreas, and bile from the liver. Acid in the duodenum also stimulates the secretion of DUOCRININ which causes a flow of enzymes from Brunner's glands. At the same time, fats entering the duodenum cause ENTEROGASTRONE to inhibit acid secretion and reduce muscular action in the stomach. Incidentally, fats also stimulate the secretion of CHOLECYSTOKININ which controls the muscles of the gall bladder (§ 3.112). When the products of protein digestion reach the duodenum from the stomach, they cause PANCREOZYMIN to stimulate the flow of enzymes from the pancreas to continue the digestion of proteins in the duodenum. When the resulting peptones reach the ileum, they cause ENTEROCRININ to stimulate there the secretion of further digestive enzymes in the succus entericus. It is therefore apparent that this series of hormones acts independently of any nervous stimulation to produce a co-ordinated series of changes in the gut, and especially in the sequence of secretions poured into its lumen, so that the phases of digestion follow one another in the right order and at the right time.

These hormones have several peculiar features in common: they are not stimulated by nerves but by direct mechanical or chemical stimuli; they are kinetic and appear in this case to be nerve-like, in that their actions are the same as those of the parasympathetic nervous system in lower vertebrates; they are all secreted by isolated cells in the gut mucosa, since no discrete endocrine glands are to be found, but their histological origin is unknown (§ 2.132). If the cells are endodermal, they are unlike those secreting any other kinetic hormones.

4.12 OVIDUCAL GLANDS

GASTROPODA. Increased formation of secretory material in the albumen gland in the reproductive ducts of the slugs, *Arion* and *Limax*, has been shown to depend on a hormone from the GONAD (Laviolette, 1956). The growth of the glands is also stimulated and it seems probable that the hormone is having a morphogenetic effect rather than the strictly kinetic action of releasing the secretion into the ducts.

AMPHIBIA. The oviducts of Anura and Urodela secrete jelly, which is laid down round the ovum and swells when it is laid in water. At first it serves a protective function, but may be eaten later by the newly-hatched young. In *Bufo arenarum* it has been shown (Smith, 1955) that injection of a variety of hormones can induce the secretion of this jelly from the oviducal glands. The most consistent results seem to be obtained with PROGESTERONE-like substances from the simple corpora lutea that form during ovulation in the ovary (Galli-Maïnini, 1951), under the morphogenetic influence of the luteinizing hormone, LH, from the adenohypophysis (§ 2.123; Table 15).

This secretion of jelly has also been induced by PROLACTIN, when supplied from implanted toad hypophyses; but this hormone has not been confirmed as physiologically active in nature. It is probably the same as luteotrophin, LSH, the action of which in mammals would be to stimulate the secretion of progesterone. If it is the same in *Bufo*, this would be one of the rare cases in which the secretion of a hormone with a kinetic action is subject to endocrinokinetic stimulation (§ 4.2); but the main function of progesterone is morphogenetic and this kinetic action seems to be subsidiary. It is claimed however that prolactin can act in the absence of the ovary (Houssay in Nalbandov, 1959).

AVES. The single oviduct of young birds secretes albumen most freely in response to stimulation by PROGESTERONE in the presence of oestrogen; in mature birds the process is facilitated by the presence of the egg yolk, though this may be replaced by any smooth foreign object such as a glass bead of suitable size (Nalbandov, 1959).

MAMMALIA. The uterus is a derivative of the oviduct, in which

Table 15. Kinetic hormones controlling other exocrine glands

	EFFECTORS	VERTEBRATE		INVERTEBRATE	
		HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
4.12	OVIDUCAL GLANDS				
	Albumen	Progesterone	*Bufo*	Gonad ?	Gastropoda
		Prolactin, LSH	,,		
	Uterine	Progesterone	Mammals		
4.13	MILK-SECRETING GLANDS				
4.131	*Increase in secretion*				
	Crop	Prolactin, LSH	Birds	—	—
	Mammary	Prolactin, LSH	Mammals		
4.132	*Decrease in secretion*				
	Crop	Oestrogen	Birds	—	—
	Mammary	Oestrogen	Mammals		
4.14	SKIN GLANDS				
	Mucus	Adrenaline ?	Amphibia	—	—
	Sweat	,,	*Equus*		
	Cuticle secreting	—	—	Ecdysone ?	Insecta

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glands hypertrophy and secrete at the time of implantation of the embryo and during early stages of its development. Not only the growth of the glands but also their secretion seem to be stimulated by PROGESTERONE from the corpora lutea in the ovary. This similarity to the hormones that are claimed to stimulate the secretion of oviducal glands in the toad, *Bufo*, may lend weight to the claim of progesterone to be concerned in the latter. It is clear, however, that there are distinct differences between the hormone pattern in the lower vertebrates and the mammals, and this line of argument must be accepted with caution.

4.13 MILK-SECRETING GLANDS

AVES. In some birds, such as the pigeon, *Columba*, a nutritive fluid, the so-called "pigeon's milk", is produced from the thickened lining of the crop in both sexes and is regurgitated to feed the unfledged young. This secretion seems definitely to be under the control of PROLACTIN from the adenohypophysis. The hormone is effective even in castrated, hypophysectomized and adrenalectomized birds (Turner, 1955); its action must therefore be direct.

MAMMALIA. PROLACTIN is also active in most mammals, inducing the secretion of milk in the mammary glands; but it is only able to act upon glands that have already been stimulated to grow and to reach a certain level of size and development of the acini by the combined action of oestrone and progesterone. It is not clear whether the action of the prolactin, LSH, is direct, as in birds, or whether the effect is due to its also stimulating the secretion of progesterone. The former seems the more probable, but, if so, it is the only example so far noted of a hormone that is able to stimulate the secretion of both exocrine and endocrine glands.

The action of prolactin is linked with that of other hormones in that the muscular release of the milk from the glands into the ducts, and so to the teats, is under the control of OXYTOCIN (§ 3.114). Other hormones must also have an effect upon milk production through their effects upon metabolism, and in particular on the level of sugars, fluid and calcium in the blood (§§ 5.2, 5.3 and 5.4).

Prolactin can apparently be inhibited by high levels of OESTRO-

GEN in the blood, such as are present towards the end of lactation or at the renewal of the oestrus cycle (Cowie and Folley, 1955). It is possible that the nervous system plays a part in the control of prolactin secretion, but there is less evidence for a psychological control over this secretion than there is for oxytocin (Fig. 3-7).

4.14 SKIN GLANDS

AMPHIBIA. The skin of amphibians is kept moist in air by the secretion of mucus from epidermal glands, which respond to the presence of ADRENALINE, at least in pharmacological doses of a mammalian preparation. The glands have a sympathetic nerve supply, and it has not been shown that the hormone plays any part in their physiological control. Under experimental conditions it is possible that adrenaline contracts muscles round the glands rather than stimulating secretion (Wastl, 1922). The same is probably true of neurohypophysial extracts which cause an outflow of secretion from the skin of *Xenopus* (Bastian and Zarrow, 1954).

MAMMALIA. In the cat, *Felis*, as in man, the sweat glands in the skin respond to the peculiar cholinergic stimulation supplied by their sympathetic nerves; they therefore do not respond to adrenaline in the blood as do other effectors, supplied by the more usual adrenergic sympathetic nerves. In the horse, *Equus*, and sheep, *Ovis*, the sweat glands respond to ADRENALINE by secretion, as the mucus glands do in amphibians (*fide* Winton and Bayliss, 1955).

4.2 ENDOCRINE GLANDS

The endocrine glands, like their exocrine counterparts, are effector organs, although the fact that their secretion passes into the blood, instead of appearing in a duct, makes their action less apparent. The hormones, which in many cases stimulate their secretion, therefore fall within the kinetic group. Since, however, a hormone which causes the secretion of another hormone has some peculiarities, it is convenient to distinguish it as an endocrinokinetic hormone, or one that is able to activate an endocrine gland.* These hormones have sometimes been referred to as either trophic or tropic especially in such compound names as gonadotrophic; but reasons have already been given (§ 1.51) for avoiding the confusion to which the use of these terms leads.

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* "Glandotrope Wirkung" has been used to express this activity in German (KARLSON, 1956); but there is no accepted English term.

It is not all endocrine glands, the secretion of which can be stimulated by hormones; but the exceptions are clear cut, at least in vertebrates. Glands formed from modified nerve cells are never so controlled, nor are the parathyroids and the insulin-secreting cells of the islets of Langerhans in the pancreas (§ 5.52); such control is very rare for any gland secreting kinetic hormones. It is almost always the glands secreting hormones with metabolic or morphogenetic actions, or both, that are controlled by endocrinokinetic hormones. Among invertebrates, the only cases so far known are glands derived from the ectoderm; but it seems more than likely that some will be found in the gonads. The vas deferens gland of Crustacea, with its morphogenetic hormone, could well be controlled by such a hormone; but neither this nor any other form of control has yet been found for it. Among vertebrates, all the endocrine glands in question are derived either from the endoderm or the mesoderm, and all are controlled by endocrinokinetic hormones from the adenohypophysis.

The action of an endocrinokinetic hormone is much more difficult to establish than that of a hormone which acts directly upon some kinetic or metabolic process, especially as it is so often found that the endocrinokinetic hormone stimulates a whole complex of metabolic processes, interference with any one of which may upset the balance of the rest, and interfere with the health and reactions of the test animal. An indication of the minimum number of experiments that are theoretically necessary to establish the interrelations of two hormones, one endocrinokinetic and one metabolic, has already been given (§ 1.6). It is rare to find animals in which the nervous system does not introduce further complexities. Often the different stages in the experimental proof have been supplied by different authors, and can only be interpreted by reference to the histological and chemical results of yet other workers. Interpretation of work upon vertebrates has been particularly beset by difficulties introduced by testing the hormones from one class of animals upon those of another.

In the cases given below, the main action of each endocrino-

TABLE 16. ENDOCRINOKINETIC HORMONES STIMULATING ENDOCRINE GLANDS

EFFECTORS		VERTEBRATE		INVERTEBRATE	
		HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
4.21	ECTODERMAL GLANDS				
4.211	*Y-organ*	—	—	Hanström's sensory pore organ ?	*Lysmata*
4.212	*Ventral glands*	—	—	Suboesophageal ganglion	Ephemeroptera
4.213	*Prothoracic glands, etc.*	—	—	Intercerebrum	*Hyalophora*
4.214	*Corpus allatum*	—	—	Brain m.n.c. ?	*Calliphora*
4.22	ENDODERMAL GLANDS				
4.221	*Thyroid*	TSH	Fish Amphibia Mammals	—	—
4.223	*Islets of Langerhans*				
	Glucagon	STH	*Gallus* *Canis*, etc.	—	—
4.23	MESODERMAL GLANDS				
4.231	*Adrenal cortex*				
	Aldosterone	ACTH	*Rattus*	—	—
	Hydrocortisone	ACTH	Most classes		
4.232	*Gonads*				
	Oestrogen	ICSH (+ FSH ?)	Mammals	—	—
	Progesterone	LSH	Amphibia ? Mammals	—	—
	Testosterone	ICSH	Most classes	—	—

kinetic hormone is stimulating the secretion of an endocrine gland. It will be noticed that, although this is often accompanied by growth of the gland, recent evidence shows that the two actions may be due not to the same hormone but to two separate, though closely similar, hormones. Reduction or inhibition of the secretion of endocrine glands is usually due to an indirect "feed-back" system, whereby the accumulation of the metabolic or morphogenetic hormone in the blood depresses the output of the endocrinokinetic hormone, which had induced that accumulation (e.g. ACH and ACTH, § 4.231).

Since these endocrinokinetic hormones stimulate the secretion of a second hormone which nearly always has metabolic or morphogenetic effects, they will be more fully understood after a consideration of the hormones that they control. The reader with little previous knowledge of hormones is therefore recommended to read Chapter 5 on metabolic hormones, before considering their control by endocrinokinetic hormones in the present chapter. Reference could well be made to each case as it arises, to which end the section numbers are given as a guide. An account of the morphogenetic hormones, and more details of the endocrinokinetic hormones which control them, will be given in Part II.

4.21 ECTODERMAL ENDOCRINE GLANDS OF ARTHROPODA

Ectodermal glands that are stimulated to secrete by endocrinokinetic hormones are few; the only glands that have so far been postulated all arise in the heads of Arthropoda (Part II).

The glands derived from ectodermal invaginations in the antennary or 2nd maxillary segments all secrete hormones which have a moult-promoting action. The fact that their secretion can be stimulated by endocrinokinetic hormones has been fully established in a number of insects, but is still uncertain in crustaceans.

4.211 *Y-organ possibly stimulated by a secretion from Hanström's sensory pore organ*

Crustacea. The Y-organ has been identified in many Crustacea and is derived from either the antennary or the 2nd maxillary segment, in whichever position is unoccupied by the excretory organ. Its hormone has both metabolic and morphogenetic actions, though the former, which concern protein metabolism (§ 5.2) and calcium distribution (§ 5.4), are intimately related to its main action as a moult-promoting hormone (Part II, § 3). Without its secretion, neither moulting nor regeneration can occur (Echalier 1956). It is inhibited, or its action is overridden, by the moult-inhibiting hormone from the sinus gland; but it can secrete when its nerve supply has been severed. This last observation suggests that it may be subject to some hormonal stimulation, such as might be exerted by Hanström's sensory pore organ, which secretes a MOULT-ACCELERATING HORMONE in *Lysmata* and *Leander*; but there is only presumptive evidence for naming the latter as a true endocrinokinetic hormone, capable of stimulating the secretion of the Y-organ (Knowles and Carlisle, 1956).

4.212 *Ventral glands stimulated by a secretion from the suboesophageal ganglion*

INSECTA. The maxillary ectodermal glands which secrete the moult-promoting hormone, ecdysone, in the more primitive orders, Ephemeroptera and Odonata, retain their original ventral position in the head (Fig. 2-8). Unlike their homologues in other orders of insects, they are stimulated to secrete by neurosecretory cells in the suboesophageal ganglion, instead of in the brain. The axons of these cells connect directly with the ventral glands (Gabe, 1953) and probably release a neurohormone (§ 1.2), since they are only effective if the axons remain intact. A rich source for extracts of the neurohormone has been found in the ganglion (Arvy and Gabe, 1954), but a vascular endocrinokinetic hormone has not been shown.

4.213 *Peritracheal and prothoracic glands stimulated by a secretion from the intercerebrum*

INSECTA. Despite the differences in their final positions (Fig. 2-8), these glands appear to be homologous with each other and to be derived from ectodermal intuckings in the 2nd maxillary (or labial) segment, like the ventral glands and some of the crustacean Y-organs. The peritracheal glands form part of Weismann's ring in Diptera, such as *Calliphora*. Prothoracic glands occur in most other genera, of which *Rhodnius*, *Hyalophora* and *Bombyx* are the only ones that need to be referred to here. These glands have all been found to secrete the moult-promoting hormone, ECDYSONE, in response to an endocrinokinetic hormone, PROTHORACOTROPHIN, from the neurosecretory cells in the intercerebrum of the brain.

It is clearly established that no nervous connection is needed between the brain and prothoracic glands for stimulation to be effective, except possibly in the Diptera. A conclusive proof for the action of an endocrinokinetic hormone in the Lepidoptera can be given in connection with the termination of diapause (§ 5.112), and is therefore more appropriate here than an example derived from the control of moulting (Part II, § 3); but the interaction of the hormones seems to be the same in either case.

In nature, diapause of the Cecropia silkworm, *Hyalophora*, lasts for 6 to 7 winter months before the tissues again become active and differentiation leads to the emergence of the adult in the spring (§ 5.12). Diapause can be shortened or "broken" artificially in various ways, of which the simplest is the injection of an active extract of ECDYSONE from the prothoracic glands. These glands do not secrete during diapause, but they can be induced to do so at any time by the presence of an actively secreting brain. Reactivation of a diapausing brain can best be brought about by chilling it suitably (Williams, 1952). If a diapausing pupa is joined by a plastic tube to a diapausing pupal abdomen, so that their influence on each other can only be by hormones in circulating haemolymph, then a chilled brain, implanted in the hinder abdomen (Fig. 4-6), breaks diapause in the anterior specimen first, and only later in the hinder abdomen, where the implant is. It may be concluded that the brain has no direct effect in the hinder abdomen, but that its endocrinokinetic hormone, PROTHORACOTROPHIN, stimulates the prothoracic glands in the anterior specimen to secrete ECDYSONE, which may override the diapause hormone, D (see § 5.112). If the length of the tube separating the two pupae is increased, the time lapse between brain implantation and the end of diapause is also increased.

The possibility that the secretion of other metabolic hormones by the prothoracic gland may also be subject to endocrinokinetic stimulation by a hormone from the brain has not, apparently,

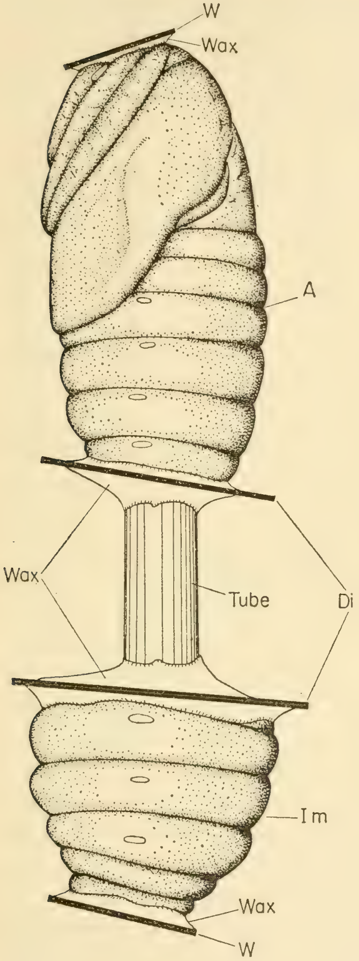

FIG. 4-6. Experimental method used to test the action of hormones in diapausing pupae of the Cecropia silkworm, *Hyalophora*. The pupa in front is joined, by a plastic tube up to 3 cm in length, to an isolated abdomen behind. The tube passes at either end through a disc (*Di*) which closes the cut surface of the abdomen, being sealed in with paraffin wax. Windows (*W*) can be sealed in at either end for observing the onset of differentiation in the internal tissues. This is stimulated by implanting a chilled, and therefore activated, brain into the hinder abdomen (*Im*); PROTHORACOTROPHIN from the implant causes secretion of ECDYSONE, the moult-promoting hormone, from the prothoracic glands in the front specimen (*A*), which reacts first. Diapause is broken later in the hinder abdomen when it is reached by the haemolymph bearing ecdysone from the front specimen (based on data from Williams, redrawn after Hinton, 1951).

been specifically investigated. Presumptive evidence in favour of such an effect is that both the metabolic and morphogenetic functions of the glands are carried out simultaneously, so that they could be due to the same prothoracic hormone under the same endocrinokinetic control.

4.214 *Corpus allatum of Insecta possibly stimulated by a secretion from the brain*

The corpora allata are ectodermal invaginations from the 1st maxillary segment (§ 2.122) and their secretion inhibits metamorphosis in the nymphal or larval and pupal stages; but it stimulates egg-growth as well as increasing oxygen consumption in the adult. The best evidence for any hormonal stimulation of their secretion is derived from experiments on the blow-fly, *Calliphora*; but the results are not conclusive.

If blow-flies, 8 hours after their emergence as adults, have their median neurosecretory cells, m.n.c., removed from the brain, it is found that the eggs in the ovary fail to mature, the result being the same as that which follows allatectomy. Reimplantation of mature corpora allata into allatectomized females can restore egg-growth to normal in 93 per cent of cases; but a similar implantation (of corpora allata) into flies deprived of m.n.c. has scarcely any effect. The reimplantation of a double dose of m.n.c. into flies deprived of their own m.n.c., but retaining their corpora allata did not cause so great an increase in egg size as the reimplantation of corpora allata into flies with normal m.n.c. (Thomsen, 1952). If these results are interpreted as showing that the neurosecretion from the brain has a stimulating effect upon secretion by the corpus allatum, then they suggest that the brain cells secrete this endocrinokinetic hormone less freely in isolated implants than when they remain *in situ* in the brain. There is no positive evidence that the brain has any control over the secretion of metabolic hormones from the corpora allata; the effect of removing the m.n.c. from the brain has not been tested in relation to oxygen consumption.

On the other hand it is clearly established that inhibition of secretion from the corpora allata can be brought about by the brain, both during metamorphosis (Part II, § 3) and while developing eggs are present in the oviducts of the viviparous cockroach, *Leucophaea maderae* (Lüscher and Englemann, 1955). Growth of the corpora allata, as well as their secretion, is released from this inhibition by sectioning the nerves from the brain. Since this operation not only deprives the corpora of nervous stimulation but also of a copious neurosecretion, which passes to them within the nerve axons from the brain and the corpora cardiaca, it is not clear whether the inhibition is nervous or secretory (Scharrer, 1952; cf. Fig. 3-2).

4.22 ENDODERMAL ENDOCRINE GLANDS OF VERTEBRATA

4.221 *Thyroid gland stimulated by TSH*

The thyroid-stimulating hormone or THYROTROPHIN, TSH (Table 16), can be extracted from the adenohypophysis of most vertebrates, including teleost fish, but not the elasmobranchs; yet all too often the hormone has been tested on an animal of a different class from that of the donor (Adams, 1946). In most cases, even when the hormone comes from the same kind of animal, the test of the efficacy of the TSH has been its action in inducing growth of the THYROID GLAND rather than in stimulating its secretion of THYROXINE, which is the aspect under consideration here.

TELEOSTEI. The most readily observed effect of thyroid secretion is its power to increase the oxygen consumption of animals in which it occurs. This can be used as an indicator of the action of TSH on the thyroid.

In most teleosts, except *Pseudoscarus*, it is extremely difficult to remove the thyroid glands, because they are so diffuse; but the same effect as thyroidectomy can be achieved by the injection of methylthiouracil, *MTU*, which destroys the thyroxine. By using this on goldfish, *Cyprinus*, before measuring their oxygen consumption for several hours under constant conditions, it could be shown that, whereas injections of TSH into normal adult fish in the summer caused an increase of up to 200 per cent in oxygen consumption, similar injections of TSH, following the use of *MTU*, were without effect (Müller, 1953). This shows that, at least in active adult fish, THYROID GLANDS are responsive to the endocrinokinetic action of TSH. It has also been shown that more TSH is required at lower temperatures to maintain the same level of thyroxine secretion (cf. Pickford and Atz, 1957). Removal of the hypophysis should not affect these results.

AMPHIBIA. One of the early discoveries about endocrine glands was that the THYROID GLAND of frog tadpoles, *Rana*, regressed and might atrophy, if the hypophysis was removed. The tadpoles then failed to metamorphose; but could be induced to do so by injections of a hypophysial extract containing THYROTROPHIN, TSH. This stimulated renewed growth of the thyroid gland and the formation and release of THYROXINE, which in turn induced metamorphosis.

MAMMALIA. It seems clear that here (and in birds, Bates and Cornfield, 1957) the discharge of THYROXINE from the thyroid into the blood circulation occurs in response to stimulation of the gland by TSH. The action is, however, not altogether simple, since evidence is accumulating for there being either two separable actions of TSH, or possibly two hormones; one stimulating the growth of the THYROID GLAND, and the other its iodine metabolism and secretion.

The cycle of iodine metabolism has been worked out in some detail, partly by means of studies on radioactive iodine (I^{131}), which can be followed through the tissues *in vivo* (Taurog *et al.*, 1958). Iodides, derived from food and from the breakdown of disused thyroxine, circulate in the blood, whence they are trapped by the thyroid gland and oxidized to iodine. (This reaction is specific and much more efficient than that by which other halogens and related elements are picked up by the thyroid.) In the gland, iodine is attached to an organic molecule to form thyroglobulin, which is a precursor of the hormone. It is stored as a characteristic colloid in the intrafollicular lumen (Fig. 4-7 *a–c*). It can then be hydrolysed by a proteolytic enzyme to release thyroxine into the circulation (Fig. 4-7 *d–e*). This filters through the capillary walls to reach the tissue spaces, and bathes the cells before being drained into the lymphatics. The thyroxine accumulates in the peripheral tissues and, notably, in skeletal muscle, where it seems to be concerned with the activity of tissue enzymes. When the tissue hormone is broken down through use, it yields up iodides to the circulation, and the cycle starts afresh (Salter, 1949).

TSH acts upon this cycle in the thyroid gland itself. Its first effect is to activate the enzyme converting the stored thyroglobulin to thyroxine, and its second is to stimulate the release of thyroxine into the circulation. This reaction is rather slow in rats, and may only be detectable histologically after 22 hr (Fig. 4-8). At the same

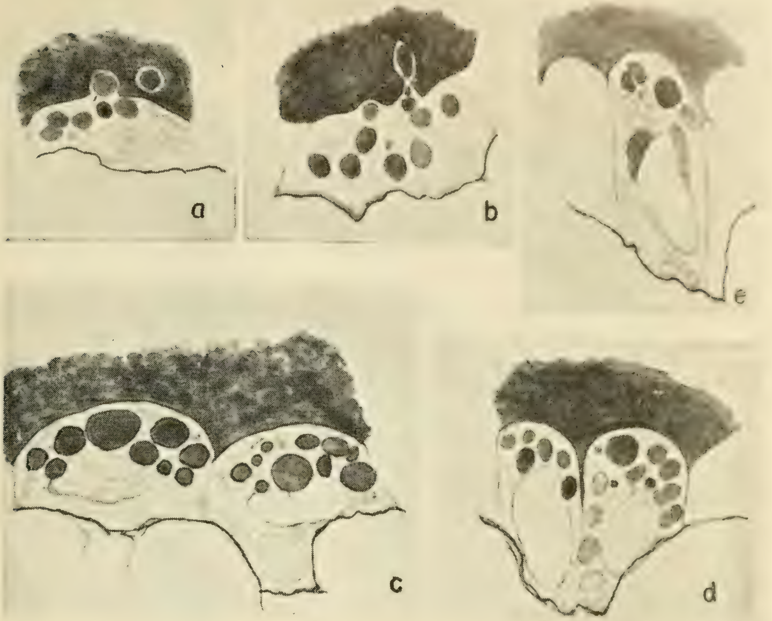

FIG. 4-7. Camera lucida drawings of sections of thyroid glands from the guinea pig, *Cavia*, rapidly frozen-dried at intervals after injecting standard doses of thyroid stimulating hormone, TSH (× 2150). (*a* and *b*) after half an hour and (*c*) after 6 hr from the time of injection, to show gradual increase in cell-size and accumulation of droplets near the inner surface of the cells, through which some are passing into the intrafollicular store of colloid above; (*d* and *e*) a later stage with increase in cell height and a reversal of the direction of cell activity. Colloid is being reabsorbed from the store as clear droplets, and secreted towards the surface of the cell next to the blood capillaries below (from de Robertis, 1949).

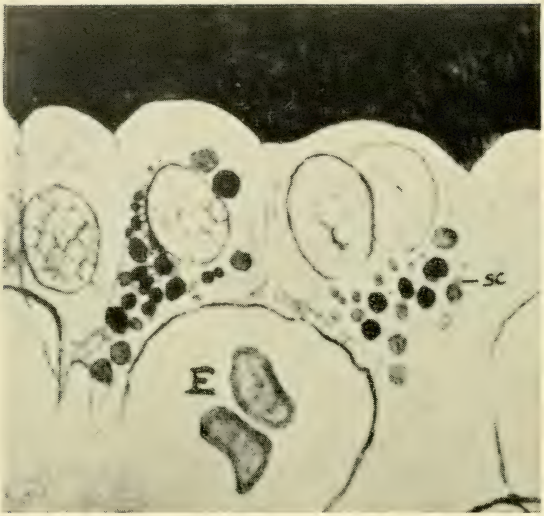

FIG. 4-8. Thyroid gland of *Rattus*, 22 hr after an injection of TSH (later stage than Fig. 4-7 *d*). The droplets of colloid (*sc*) from the intrafollicular store (above) have all moved nearer to the secreting surface, which is extended towards the lumen of the blood capillary (*E*). (From de Robertis, 1949).

time, trapping of iodides and the formation of the intrafollicular colloid is stimulated; although the amount trapped depends upon the level already in store (Barker, 1955). In the absence of TSH, both trapping of iodine and secretion of THYROXINE may be reduced to 10 per cent of normal in 5 days; the binding of iodine to the colloidal proteins may fail or proceed only slowly, and in some cases diiodotyrosine (or even monoiodotyrosine) is formed instead of thyroxine. It has been shown that TSH is inactivated *in vitro* by exposure to thyroid, but not to other tissues; and that it can be re-activated by treatment with reducing agents such as thiouracil. This may be related to the fact that the latter destroys the thyroxine in the thyroid.

The increase in height of the follicular epithelium in the thyroid gland, which is often used as a means of assay for TSH activity, accompanies the normal release of thyroxine from the gland (Fig. 4-7 *d–e*); but increase in weight of the gland is not necessarily related to its rate of secretion, though it may also follow prolonged treatment with TSH (or with the growth-promoting fraction thereof).

The rate of secretion of TSH, rather than the quantity of it that is stored in the hypophysis, seems to be increased by some form of control from the hypothalamus, since it can be disturbed and reduced by hypothalamic lesions in the brain (Bogdanove, 1957). On the other hand, its secretion can be decreased by high concentrations of thyroxine, circulating in the blood; this feed-back reaction tends to maintain a steady level of production of the metabolic hormone.

Evidence for there being two distinct, though closely similar, substances both included under the name of thyrotrophin is provided by experiments on mice, in which the growth-promoting action of TSH responds differently from its secretion-promoting action. Hypophysectomy results in reduction in size of the thyroid gland, as well as in its secretion. If the hypophysis is transplanted elsewhere in the body, the mice do not show any increase in thyroid weight, when compared with hypophysectomized controls; but such reimplantation does restore the iodine content and thyroxine formation and secretion by the thyroid glands to 66 per cent of normal, as compared with only 10 per cent in hypophysectomized controls without implants (Greer, Scow and Grobstein, 1953). The growth-promoting action of TSH is only restored to any appreciable extent if the reimplantation of the hypophysis brings it into contact with the median eminence of the brain, in the position from which it was originally removed. This may be compared with the similar effect of *CRF* upon the growth-promoting actions of other hypophysial hormones (§ 4.323).

4.222 *Parathyroid glands*

Earlier work suggested that activity of the parathyroid glands could be stimulated by thyroxine from the thyroids. It is now established that this is not an endocrinokinetic action, but an indirect effect, in that thyroxine tends to lower the calcium and increase the phosphate content of the blood and these changes both stimulate the parathyroid glands directly (§ 5.521).

4.223 *Glucagon-secreting cells of the pancreas stimulated by STH*

AVES. The growth hormone or SOMATOTROPHIN, STH, has only been shown to induce an increase in blood-sugar in the chick, *Gallus*; but it seems probable that this is an indirect action brought about through its endocrinokinetic stimulation of GLUCAGON secretion, as in some mammals (§ 5.211).

MAMMALIA. The stimulation of GLUCAGON secretion from α cells in the islets of Langerhans (§ 2.222) is not yet fully understood, nor is glucagon widely distributed in mammals (§ 5.2). Though some may be active in all mammals, it is only in some carnivores (cat and dog, but not ferret) that it has been found to be the main factor in raising the level of blood-sugars, in response to stimulation by hypoglycaemia (Saka, 1952) or by SOMATOTROPHIN or growth hormone, STH*, from the adenohypophysis (Young, 1945). The evidence for the endocrinokinetic action of STH has been somewhat obscured by the fact that its administration to hypophysectomized dogs and cats gives different results at different ages. In young animals the resulting release of sugar can all be consumed in growth, and the stimulation of the latter is the only observable result; but in older animals, when growth has ceased, the stimulation of glucagon secretion and the consequent release of sugar into the blood is not masked, and hyperglycaemia, or diabetes mellitus, results and may even become permanent (cf. § 5.211).

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* Glucagonotrophin would be more descriptive in this context.

4.23 MESODERMAL ENDOCRINE GLANDS OF VERTEBRATA

4.231 *Adrenal cortex stimulated by ACTH*

In most vertebrates there is some evidence that the secretion of CORTICAL HORMONES is stimulated by ADRENOCORTICOTROPHIN, ACTH, from the adenohypophysis. Since the actions of the cortical hormones are mainly metabolic, there is no doubt here, as there can be with the thyroid, that the endocrinokinetic hormone is in fact stimulating the secretion of metabolic hormones, and not only of morphogenetic hormones.

The stimulation of the adrenal cortex by ACTH presents an interesting problem. Although the actions of cortical hormones connected with electrolyte and water balance all lead to concentration of salts in the blood, it is clear that two distinct types of hormone are involved: the ALDOSTERONE-LIKE HORMONES which increase salt reabsorption (§ 5.311), and the HYDROCORTISONE-LIKE HORMONES which mainly cause water diuresis (§ 5.321). Nevertheless, the tentative suggestion that there may be more than one hormone in ACTH only indicates a separate control for increasing the weight of the adrenal cortex from that inducing its secretion. There appears to be no indication of separate hormones for stimulating the secretion of the different hormones from the cortex (Munson and Briggs, 1955). Most authors, however, still support the view that adrenocorticotrophin, ACTH, is a single substance (Astwood, 1955).

Secretion of aldosterone-like hormones from the adrenal cortex

Aldosterone is chemically quite distinct from the other cortical hormones in having an 18-aldehyde group in the molecule. It is biologically very active in stimulating salt retention or reabsorption by the kidneys, although it is secreted in relatively minute quantities. Little is known of the means by which its secretion is controlled; but there is some evidence that it is secreted in response to stimulation by ACTH in the rat, though not in man (Simpson and Tait, 1955). Elsewhere it appears to be directly stimulated by a lowering of salt concentration in the blood.

Secretion of hydrocortisone-like hormones from the adrenal cortex

COLD-BLOODED VERTEBRATA. There is apparently not much direct evidence of ACTH stimulating secretion by the ADRENAL CORTEX in vertebrates other than mammals, although growth of the adrenal tissue, or of the anterior interrenal tissue which is its main homologue in fish, has been established in relation, not only to mammalian ACTH, but also to extracts of a similar fraction from the hypophysis of fish (Pickford and Atz, 1957). There is some evidence (§ 5.411) that in *Astyanax* the secretion of cortical hormones can continue in the absence of ACTH (Rasquin and Rosenbloom, 1954); but the rate of secretion does not seem to have been measured. ACTH derived from the pituitary of the salmon, *Salmo salar*, causes reduction of ascorbic acid in the rat, but has not been tested on fish (Rinfret and Hane, 1955).

MAMMALIA. The HYDROCORTISONE-LIKE HORMONES, ACH (sometimes referred to as the glucocorticoid hormones, from their diabetogenic action on carbohydrate metabolism), are the most abundant secretions from the adrenal cortex. In normal circumstances the release of ACH from the cortex into the blood is continuous, but it has a slight diurnal rhythm of change in rate. In the human, for instance, this is lowest at night and highest in early morning. In response to any stress, or tissue damage, there is an immediate increase in the rate of secretion. Since small injections of ADRENOCORTICOTROPHIN, ACTH, from the adenohypophysis, can influence the rate of secretion, it is thought that there is also a basic rate of secretion of this endocrinokinetic hormone, but that it can very quickly be increased in response to damage or stress, and that this induces the cortical reaction (Munson and Briggs, 1955).

Secretion of ACH from the cortex is accompanied by a marked loss of ascorbic acid (as well as of cholesterol and a sudanophilic substance, Fig. 4-9), which is not replaced until more hormone is synthesized. The amount of the acid present at any time can be assayed in the frozen glands of rapidly killed specimens. Its disappearance under stress provides a measure of the hormone secretion, which follows it closely (Slusher and Roberts, 1957). It can, therefore, be used as an indication of the rate of ACTH secretion. The reaction varies with the exact type, duration and severity of the stress. If, for instance, anaesthetized rats are given some relatively mild noxious stimulus, such as haemorrhage or an injection of histamine, or if normal rats have a bout of severe exercise, ACTH is released and causes a rapid increase in the amount of circulating adrenocortical hormone, ACH, revealed by a reduction in adrenal ascorbic acid (Fig. 4-9). In these cases recovery occurs within 24 hr. In more severe stress, depletion of ACH may be so complete that recovery may not be possible, and death results.

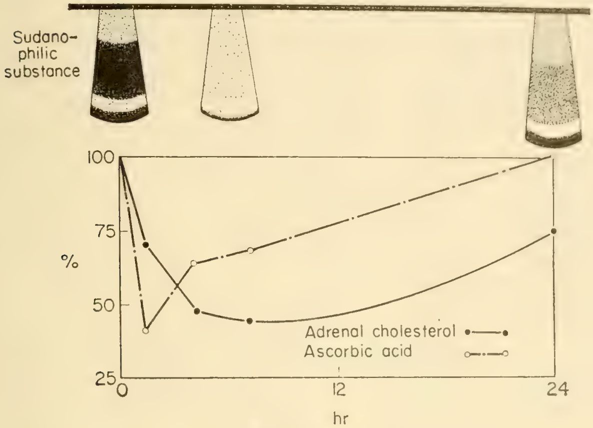

FIG. 4-9. Diagram to show the type of change that occurs in the adrenal cortex, following brief secretion of ACTH from the adenohypophysis, induced by non-fatal haemorrhage for 1 hr. The sectors of gland, above, indicate the change in its size and in the amount of its sudanophilic content. The ascorbic acid (○) and cholesterol (●) in the gland are graphed in percentages over a 24 hr period. These and the sudanophilic substance show a sudden drop in response to the ACTH stimulus at hour 0 until the end of stress at hour 1; this corresponds with the release of the whole store of cortical hormone. During the rest of the 24 hr the store is gradually built up again. Similar effects can be produced by a sudden bout of exercise, or an injection of histamine or of ACTH itself (from Sayers and Sayers, 1949).

The release of ACTH is also related to the amount of ACH already in circulation; when the latter is high it inhibits further

ACTH secretion by the usual type of "feed-back" reaction, tending to maintain a steady level. If, therefore, an injection of ACH precedes a histamine injection, it is able to block the secretion of ACTH. There is then no reduction in ascorbic acid, as compared with the control (Fig. 4-10). This result can be achieved, even though the ACH injection precedes the histamine by as little as 2 sec, or just sufficient time for the ACH to reach and affect the source of ACTH in the adenohypophysis.

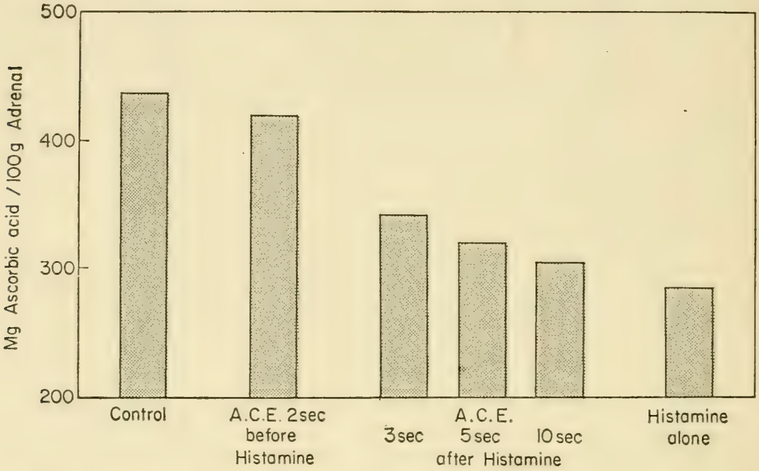

FIG. 4-10. Ascorbic acid remaining in the adrenal cortex, of six groups of rats, killed shortly after receiving injections. Control rats were given saline injections; the others had all been given similar injections of histamine, sufficient to produce a noxious, but not a fatal, stimulus. The marked lowering of ascorbic acid due to histamine alone, which elicits full secretion of ACTH from the hypophysis, is shown on the right. Additional injection of an adrenal cortical extract, A.C.E., 3 to 10 seconds *after* the histamine has practically no effect upon this lowering of ascorbic acid. A similar injection of A.C.E., given 2 seconds *before* the histamine, is able to block ACTH secretion, so that the histamine injection produces practically no more response than the saline given to the controls. As in Fig. 4-9, the loss of ascorbic acid corresponds to release of ACH from the adrenal cortex (from Munson and Briggs, 1955).

By reversing the order of the intravenous injection of the histamine and the cortical hormone, and varying the time interval between the two injections, it can be shown that in 10 sec the histamine has already exerted almost as great an effect upon the release of ACTH and the reduction of ascorbic acid, as it does in the absence of any cortical injection (histamine alone, Fig. 4-10). After only 3 sec there is practically no blocking effect by the cortical hormone, so that it can be concluded that the histamine has already produced some effect upon the hypophysis. The action is in fact almost as rapid as that of the cortical hormone itself, and takes little longer time than the blood needs to circulate from the point of injection to the hypophysis. This does not, however, solve the question of whether these substances act upon the hypothalamus of the brain, rather than upon the hypophysis direct.

It is interesting to note that the time required for ADRENALINE to produce a similar reaction in the hypophysis is considerably longer than that for histamine (Fig. 4-11). Adrenaline cannot therefore be held to act as a necessary intermediary between the noxious stimulus and the adenohypophysis from which it calls forth the ACTH secretion (Munson and Briggs, 1955).

The rate of secretion of both ACTH and of the cortical hormone can also be measured directly in the blood. ACTH can be detected in circulation soon after the application of any noxious stimulus; ACH can be detected in the adrenal vein within a few seconds of the injection of ACTH. But this method of assay is not wholly satisfactory, since both hormones are destroyed in the tissues within a few minutes of their release. It has been estimated that ACTH is reduced to about half its previous concentration in 2 to 5 min in the blood; but its fate is somewhat uncertain. It is not excreted in the urine, but accumulates in even larger quantities in the kidneys than in the adrenal cortex. It is inactivated after incubation with kidney or liver tissue *in vitro*; yet the removal of both kidneys and most of the liver does not render an ACTH injection any more effective than before, in reducing the ascorbic acid contents of the adrenal cortex, possibly because even small doses can produce a maximal effect (Astwood, 1955). In the dog, the action of ACTH, in increasing ACH secretion, persists for about 15 min after injection; and even an hour after removal of the hypophysis and the source of ACTH, the naturally induced secretion of ACH is only reduced to one half.

4.232 *Gonads stimulated by gonadotrophic hormones*

Morphogenetic hormones, secreted by the gonads, have a variety of effects related to reproduction, and have been reported from many animals, including an unusually wide range of invertebrates as well as vertebrates. So far, it is only in the vertebrates that the secretion of these gonadial hormones is known to be controlled by endocrinokinetic hormones. Like the other hormones of this type in vertebrates these are all secreted from the adenohypophysis; they are often referred to as gonadotrophins, in common with

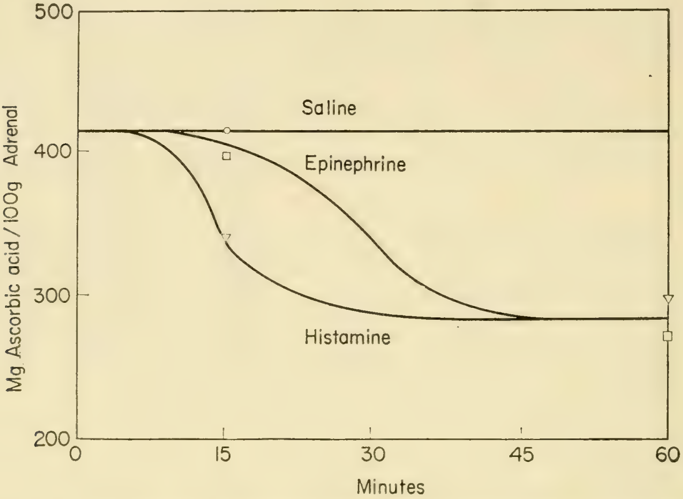

FIG. 4-11. Effects of injections of saline, epinephrine (adrenaline) and histamine on the ascorbic acid content of the adrenal cortex of rats, in mg/100 g gland (ordinates). The saline causes no change in 60 min (abscissae); the reduction due to adrenaline and histamine is by then the same, showing the two doses to be equivalent. The effect of histamine is much the more rapid, and must therefore evoke secretion of ACTH directly and not through any intermediary action of adrenaline (cf. Fig. 4-10, based on similar experiments). (From Munson and Briggs, 1955).

other hormones from the same source which have marked morphogenetic effects upon the growth of their target organs. Only those causing secretion of endocrine glands need be treated in the present section; although all the gonadotrophic hormones play an important rôle in relating breeding cycles to seasonal stimuli from the environment (§ 4.232 and Part II, § 4). The gonadial hormones themselves are mainly morphogenetic in action (§ 1.53); but they are peculiar in having some subsidiary kinetic effects (§§ 3.12, 4.12 and 4.324). In their latter capacity they provide the only examples of kinetic hormones which are controlled by endocrinokinetic hormones.

Information regarding the gonadotrophic hormones of the cold-blooded vertebrates is scanty, compared with that concerning birds and mammals; but in general they appear to have similar effects upon the secretion of the gonadial hormones (Pickford and Atz, 1957). Further reference will be made to them in relation to the latter (Part II, § 4).

Interstitial cells in the testis stimulated by ICSH

In birds and mammals, and probably in most other vertebrates, the release of testosterone, or other androgenic hormones, from the testis is brought about by an endocrinokinetic INTERSTITIAL-CELL-STIMULATING HORMONE, ICSH, secreted from the adenohypophysis. The control of its secretion, like that of TSH, comes from the hypothalamus of the brain and can reflect the effects of environmental changes, transmitted to the brain either directly or by the eyes. The secretion of ICSH, by its release of testosterone, fires off the whole chain of events associated with the breeding cycle in the male. In birds these can include migration, courtship and nest-building and the appearance of secondary sexual characters of plumage and wattles, as well as the essential development of the genital ducts. In mammals corresponding changes in behaviour and structure are brought about by similar hormones; in those with a limited breeding season there is a slow feed-back mechanism, whereby the accumulation of testosterone inhibits further ICSH secretion after a few months. In those species with continuous breeding this inhibition is not effective, at least until extreme old age.

Follicle cells in the ovary stimulated by ICSH

The release of oestrone, or other oestrogenic hormones, from the vertebrate ovary appears also to be stimulated primarily by the INTERSTITIAL-CELL-STIMULATING HORMONE, ICSH. Its action may depend in some cases on the synergic effect of the FOLLICLE-STIMULATING HORMONE, FSH; but the most important action of the latter is to cause the growth of the follicle cells, along with that of the ovum that they enclose. There are differences in the relative importance and effects of these hormones between different species and even more between different classes of vertebrates.

The release of oestrogens by ICSH results in the development of the female genital ducts, but not as a rule in that of any secondary sexual characters; the external appearance of the female is usually distinguishable from the male by the absence of male characters, rather than by any positive features due to oestrogenic hormones.

In the female mammal, whether the breeding season is short or continuous, there is always an alternation, or cycle, of phases within the breeding period and of these it is the oestrus phase which results from the secretion of oestrogens (§ 4.323). The feed-back reaction, whereby the accumulation of oestrogens decreases ICSH secretion, is relatively rapid in the female and makes way for the alternate phase of the cycle, whether this is dioestrus, pregnancy or pseudopregnancy. In most species oestrus only lasts for a few days each time.

Corpora lutea in the ovary stimulated by LSH

MAMMALIA. The endocrinokinetic hormone LUTEOTROPHIN, LSH, from the adenohypophysis, stimulates the secretion of progesterone from the corpora lutea that form in the ovarian follicles after the shedding of the ova. LSH is probably the same as PROLACTIN, which causes the secretion of milk from crop and mammary glands (§ 4.13); if it is the same it is the only one of the endocrinokinetic hormones which has the power to stimulate any exocrine glands as well as an endocrine gland (§ 4.323). It can only affect the corpora lutea after their growth has been stimulated by the morphogenetic LUTEINIZING HORMONE, LH, also from the adenohypophysis. Incidentally, LH was for many years confused with ICSH; but there is now good reason to believe that they are distinct and that while ICSH occurs in both sexes, LH is normally present in the female only. Its occurrence throughout life can be completely inhibited if a testis, either natural or implanted, is present during the development of an animal of either sex (Witschi, 1955).

The action of LSH, by inducing the secretion of progesterone, initiates the alternate, or dioestrus, phase of the female cycle, a phase which makes pregnancy possible and for which there is no hormonal counterpart in the male.

This may not have been the primary function of progesterone, for it occurs in association with viviparous development in many vertebrates besides mammals; it is probably under the same endocrinokinetic control throughout (Matthews, 1955).

Interaction of gonadial and endocrinokinetic hormones in reproduction

In the sexual reproduction of all vertebrates there is need for the gametes to ripen simultaneously in males and females of the same species, and for the young of most land forms to be produced at a suitable season of the year for their early growth. The endocrinokinetic hormones play a vital rôle in bringing this about.

MAMMALIA. In placental mammals the viviparous development of the young embryo in the maternal uterus and its subsequent nourishment from the mammary glands increase the complexity of the situation, so that several more hormones are needed to control reproduction in the female than in the male.

In the male, the secretion of TESTOSTERONE is induced by ICSH, and maintains the reproductive ducts and the accessory organs in a steady, active state, as well as developing secondary sexual characters, such as antlers. At the same time the morphogenetic hormone, FSH, ensures the continuous ripening of sperm. In species with a limited breeding season, like deer, the onset and ending of these hormone-controlled changes appears to be related by the brain to environmental factors, such as temperature and length of daylight.

In the female placental mammal at least three pairs of hormones are involved, the two members of each pair acting alternately to control the changes associated with the alternation of oestrus and dioestrus phases. The latter group are also active during pregnancy. In the oestrus phase the endocrinokinetic hormone is ICSH and the morphogenetic hypophysial hormone is FSH, as in the male; but the gonadial hormone is an OESTROGEN. In the dioestrus phase these are replaced respectively by LSH, LH and PROGESTERONE, for which there are no counterparts in the male. Their detailed actions, interactions and variations will be discussed in relation to reproduction (Part II, § 4). OXYTOCIN from the neurohypophysis also plays a part in the reproductive processes in the female; but its main actions have already been mentioned, being concerned with muscular contraction in parturition (§ 3.113) and with the action of the myoepithelial cells in bringing about "milk let-down" from the mammary glands (§ 3.114). PROLACTIN that stimulates the secretion of the mammary glands seems to be identical with LSH, although its action here is so different (§ 4.13). Even this list of seven or eight hormones involved in the reproductive activities of the female takes no account of the hormones which must actively adjust the maternal metabolism to meet the demands of gestation and lactation.

4.3 GENERAL CONSIDERATIONS

As the account of the kinetic hormones is now as complete as space allows, it will be well to review their general characteristics and the means by which their own secretion is induced, before passing on to a consideration of the metabolic hormones, which fall into so different a category (§ 5).

4.31 CHARACTERISTICS OF KINETIC HORMONES

The kinetic hormones controlling the reactions of muscles and glands in vertebrates have much in common with each other and they may even be identical, whereas those controlling the pigmentary effectors are usually distinct and differ from the former in various ways which may in part be due to the nature of the effectors concerned. Gastrin, progesterone and adrenaline are among the hormones which can control the activities of both muscles and exocrine glands. Among invertebrates there are several examples of hormones controlling muscles, but as yet none have been found to control secretion of any exocrine glands in these animals, so that there is no overlap; its investigation might be interesting.

The control of the secretion of endocrine glands is usually separate from that of other glands; but even here there is an exception in that prolactin can stimulate the exocrine mammary glands as well as the endocrine corpora lutea of the ovary.

Apart from adrenaline, the hormones controlling pigmentary effectors do not overlap with the foregoing at all, unless the hormone that stimulates dispersion of pigment in the stick insect, *Carausius*, should prove to be the same as that which stimulates locomotor activity in *Periplaneta*, since both come from the suboesophageal ganglia. There is also a difference in the number of hormones involved; the control of pigmentary effectors, and particularly of chromatophores with movable pigment, is nearly always achieved by the interaction of a pair of antagonistic hormones (§ 3.24), but the same can rarely be said of muscles or glands. The only unequivocal case of a pair of hormones is gastrin and enterogastrone, which have opposing actions on both the peristaltic muscles and the acid-secreting cells of the mammalian stomach (§§ 3.112 and 4.11). Even the apparently opposed actions of progesterone and oxytocin on uterine muscle may not be direct inhibition and stimulation, but rather a case of the presence of progesterone rendering the muscle insensitive to oxytocin throughout gestation. Nearly all the other kinetic hormones, acting upon muscles, myoepithelial cells and glands, serve to stimulate these effectors, for which there are no known inhibitors. A general inhibition of locomotion seems to be the action of an eyestalk hormone in some Crustacea, and for these no stimulator is known (§ 3.12). Elsewhere different effectors react differently to the same hormone, some being stimulated and others inhibited. This occurs with cholecystokinin, which causes contraction of the main muscles of the gall bladder but relaxation of the sphincter muscles, and with adrenaline, which contracts the intestinal sphincters and inhibits the peristalsis of the longitudinal muscles. In the frog, adrenaline has been reported to have opposite effects upon the same muscle at different dosages; this suggests that the other cases might be accounted for by different threshold levels of sensitivity. It seems more likely, however, that there may be some specificity in the muscles themselves, akin to the differentiation of many visceral muscles into those which are sensitive to sympathetic stimulation and those which are inhibited by it, but are usually sensitive to parasympathetic stimulation (Rosenblueth, 1950).

Otherwise the apparent lack of inhibitor hormones may partly be because muscles and myoepithelial cells give an all-or-none reaction to stimulation and remain indefinitely quiescent in its absence; no intermediate state of contraction of any given cell can be achieved by a balance between stimulating and inhibiting factors, such as can arrest the pigment in a chromatophore at any position between the extremes of dispersion and concentration. Graded responses might seem more probable for glands; but it may well be that a similar all-or-none reaction to that in muscles holds good also for the individual secreting cells within the gland, and that changes in rate of secretion depend upon the number of cells induced to release their secretory products into the gland lumen.

When kinetic hormones control chromatophores the effect is usually rather slow; but the rate differs in different organisms and may depend chiefly upon the concentration of the hormone reaching the effector in any given case. In achieving and maintaining a protective background response, or in adapting an eye to changes in daylight intensity, a slow response may be an advantage in preventing sudden and conspicuous changes.

Muscles and glands often show rapid responses to kinetic hormones, and may complete their reactions in a matter of minutes or even seconds, like the response to heart-accelerators (§ 3.111), or to oxytocin inducing milk "let-down" (§ 3.114), or to ACTH stimulating the release of ACH (§ 4.231). In such cases the only limitation on the speed of reaction seems to be the time that the hormone takes to pass in the circulation from its source to the effector. The effector, once stimulated, can react as quickly to a hormone as to a nerve impulse. In the case of rhythmically contracting muscles, like those of the heart or those causing gut peristalsis, the increase in rate of contraction caused by a hormone can persist for some time without further release of hormone, if the latter is only slowly destroyed in the tissues. This type of effect can clearly relieve the nervous system from a considerable expenditure of energy, on repeated impulses. This control of the level of activity may be one of the most important general functions of kinetic, or perhaps of all, hormones.

4.32 STIMULATION OF THE SECRETION OF KINETIC HORMONES

Most kinetic hormones are secreted in response to stimulation that is either direct or nervous. As far as the present evidence goes it is rare for the stimulus to come from another hormone or to be absent altogether.

4.321 *Direct control of isolated cells in the gut*

Direct stimulation can be brought about by mechanical or chemical stimuli without any intervention by the nervous system. The hormones from the gut mucosa of mammals are stimulated in this way, either by mechanical distension of the stomach walls or by the presence of acids or the products of digestion in the lumen (Table 17). The integrated, self-regulating control of digestion, which is brought about by a succession of these hormones has already been pointed out as a specialized feature of mammals (§ 4.113). The cells which secrete these hormones have not been identified; but they are assumed to occur singly in the mucosa from which the hormones can be extracted, as there is no sign of any endocrine glands there. They might be neurosecretory cells, such as secrete so many other kinetic hormones; but no other neurosecretory cells have been shown to be directly stimulated as these cells are, without any connection with the nervous system. On the other hand, if the cells are endodermal they would be like the only other hormone-secreting cells which can be directly stimulated, i.e. those which secrete metabolic hormones from the parathyroids and the islets of Langerhans (§ 5.521).

The fact that the action of these hormones is performed by the parasympathetic nerves in cold-blooded vertebrates is in favour of the former postulate.

TABLE 17. MEANS OF CONTROLLING

SOURCE OF HORMONE	NAME OF HORMONE	MEANS OF CONTROL	KIND OF CONTROL*	SECTION NO.
4.321 *Direct control of isolated cells in the gut*				
Mammalia				
Duodenum	Cholecystokinin	fats	+	3.112
Stomach	Gastrin	distention	+	4.111
Duodenum	Secretin	acid	+	4.111
Duodenum	Pancreozymin	peptones	+	4.111
Duodenum	Duocrinin	acid	+	4.111
Intestine	Enterocrinin	food ?	+ ?	4.111
Duodenum	Enterogastrone	fats	+	4.112
4.322 *Nervous control of secretory cells of nervous origin*				
Cephalopoda				
Epistellar body	Muscle tone increaser	nerve	?	3.12
Crustacea				
Pericardial organ	Heart-accelerator	nerve	?	3.111
Sinus gland	RPDH, etc.	nerve	+	3.222
Sinus gland	PLH, etc.	nerve	+	3.223
Commissures	RPCH	nerve	?	3.222
Commissures	PDH, etc.	nerve	?	3.223
Hanström's sensory pore organ	Moult-accelerator	nerve	?	4.211
Insecta				
Suboesophageal ganglion	Pigment-disperser	nerve	+	3.221
Corpora cardiaca	Heart-accelerator	?	?	3.111
Brain	Prothoraco-trophin	nerve	+ ?	4.213
Vertebrata				
Adrenal medulla	Adrenaline (muscles)	nerve	+	3.11
,, ,,	,, (chromato-phores)	nerve	+	3.223
,, ,,	,, (skin glands)	nerve	+ ?	4.14

* + = stimulation of hormone secretion
— = inhibition of hormone secretion

THE SECRETION OF KINETIC HORMONES

SOURCE OF HORMONE	NAME OF HORMONE	MEANS OF CONTROL	KIND OF CONTROL*	SECTION NO.
Neuro-hypophysis	Oxytocin (uterine muscle)	nerve	+ ?	3.113
,, ,,	,, (myoepithelial cells)	nerve	+	3.114
,, ,,	ADH (pressor action)	nerve	?	3.115
4.323 *Nervous or other control of ectodermal glands*				
Vertebrata				
Adenohypophysis,				
pars intermedia	B (MSH)	nerve	+	3.223
pars tuberalis	W (MCH)	nerve	+	3.223
pars distalis	LSH, prolactin	nerve	?	4.13
,, ,,	LSH, luteotrophin	nerve	?	4.232
,, ,,	TSH, thyrotrophin	nerve or *CRF*	+ ?	4.221
,, ,,	,, ,,	thyroxine	—	4.221
,, ,,	STH, somatotrophin	?	?	4.223
,, ,,	ACTH, adrenocorticotrophin	nerve, *CRF* or histamine	+	4.231
,, ,,	ACTH	ACH	—	4.231
,, ,,	ICSH, interstitial-cell-stimulating	nerve	?	4.232
4.324 *Hormonal control of endocrine glands*				
Vertebrata				
Gonad, testis	Testosterone (somatic motor muscle tone)	ICSH	+	3.12
Gonad, ovary	Oestrogen (somatic motor muscle tone)	ICSH	+	3.12
Gonad, ovary	Progesterone (oviducal gland secretion)	LSH	+	4.12

? = control uncertain

4.322 *Nervous control of secretory cells of nervous origin*

Many hormone-secreting cells derived from the nervous system are neurosecretory cells. These seem always to retain an intimate contact with it (§ 2.11); positive evidence of nervous control of the release of secretion from these cells is limited to a few cases only, but it may well be true of all. The main doubt is as to how the control is achieved; perhaps it is only a question of degree which determines at what point in a series of neurones the transmission of a stimulus from one to another ceases to be a nerve impulse, with a minute release of the appropriate chemical substance at the nerve endings, and becomes the release of a microscopically visible amount of neurosecretion, passing down the axon and activating the cells with which the axon is in contact. Technically the two are hard to separate, since section of the axon stops the flow of the chemical as completely as it stops the passage of the nerve impulse. Since in either case activation only passes to the immediately adjacent neurosecretory cell, a hormone (in the sense of a substance circulating in the blood) is not produced, though a neurohormone might be. Nervous stimulation of hormone secretion from the neurosecretory cell is most likely; but in any case the process remains distinct from the stimulation of gland cells by endocrinokinetic hormones in the circulation (§ 4.323).

All too often the action of kinetic hormones has only been shown in extracts, and the effect of the nervous system upon their natural secretion has been neglected. Yet there is often evidence, presumptive or actual, for an action of the nervous system on the effectors, although they are under the intermediate control of kinetic hormones; for they produce responses that are so closely related to environmental factors that it seems as though the nervous system must be involved (Table 17). Examples of this are to be seen in both crustaceans and vertebrates, the chromatophores of which respond to changes of background that can only stimulate hormone secretion indirectly through the eyes (§ 3.222); or in *Carausius*, the pigment cells of which only respond to the effect of moisture on the skin, if the ventral nerve cord is intact (§ 3.121).

The neurosecretory cells in the brain of insects, which are the sources of the endocrinokinetic hormones stimulating secretion by the prothoracic glands, and possibly by the corpora allata, are probably also under nervous control. The action of climatic and other factors upon the brain certainly determines whether or not these activating hormones are released; but this is best seen in relation to the morphogenetic actions of the moulting hormones. There the brain hormone, prothoracotrophin, determines the time of larval moults by stimulating simultaneous secretion from both the prothoracic glands and the corpora allata; but it determines the change-over to metamorphosis by activating the prothoracic glands alone (Part II, § 3).

In the crustacean brain little is as yet known of the activation of the neurosecretory cells ending in Hanström's sensory pore organ, but they may be assumed to be influenced by the nervous system like other cells of the same sort. Their endocrinokinetic activity is not yet fully established (§ 4.211).

In vertebrates nervous stimulation of secretory cells of nervous origin is well authenticated for the adrenal medulla, which maintains its connection with the sympathetic nervous system, from which its cells are derived (§ 2.114). The situation in the neurohypophysis (§ 2.114), which derives its secretion from the neurosecretory cells in the brain, is less clear. There is good presumptive evidence for nervous control of the secretion of OXYTOCIN to cause contraction of myoepithelial cells (Fig. 3-7). Moreover, it is clear that afferent nerve pathways lead through the brain to the neurosecretory cells in the supraoptic and paraventricular nuclei in the hypothalamus. These cells release oxytocin, which is then stored in the neurohypophysis; but the action of the nervous system on the neurosecretory cells is naturally difficult to investigate. Section of the neurohypophysial stalk provides no more answer to the problem than removing the neurohypophysis altogether, since it merely separates the store of the secretion from its source and leaves the source in contact with the rest of the brain. It has already been observed that after removal of the neurohypophysis, sufficient oxytocin can be released from the hypothalamus to ensure parturition (§ 3.113). An investigation of VASOPRESSIN, ADH, from the same nuclei in the hypothalamus would suffer from the same difficulties; but the action of ADH in contracting blood vessels may well be accidental, and the means for stimulating its secretion be linked to its metabolic purposes, for which it is certainly under nervous control (§ 5.322). It has been maintained that oxytocin and ADH are always secreted in the same proportions and may either be combined in one molecule or be linked to the same inactive matrix. More recently it has been claimed that the ratio between the two hormones can be appreciably changed in the neurohypophysial secretion, since electrical stimulation of the supraoptic nucleus releases a secretion with a ratio of oxytocic to ADH activity of 4:1, whereas suckling releases a secretion with a ratio of 100:1 (Harris, 1955).

Nothing is known of the way in which the endogenous heart-accelerating hormone from the gland cells of the insect corpora cardiaca (§ 2.113) is stimulated, since its presence does not depend upon either the neurosecretion or the nerves from the brain; but neither is it known if this substance from the corpora has a true physiological action (§ 3.111).

4.323 *Nervous or other control of ectodermal glands*

There are no kinetic hormones in invertebrates secreted from ectodermal cells other than nerve cells. In vertebrates, they are confined to the adenohypophysis, which is derived from the stomodaeum (§ 2.123). This is the anterior lobe of the pituitary and includes the pars tuberalis, the pars intermedia and the pars distalis. The first is the source of the melanophore concentrating hormone, W, in Amphibia, and the second is the source of the antagonistic dispersing hormone, B. Both are secreted in response to stimulation of the eyes and must have a direct nerve connection with the brain. The pars intermedia has no nerves in mammals (Fig. 2-12); but it appears to secrete intermedin and may affect morphological, rather than physiological, colour changes.

The kinetic hormones secreted from the pars distalis of the adenohypophysis are all endocrinokinetic, apart from prolactin, LSH, which stimulates the exocrine mammary glands as well as the endocrine corpora lutea. In most mammals the stimulation of these two glands would seem to alternate rather than to be linked, in that the mammary secretion of milk follows at the end of pregnancy, when the secretion of progesterone from the ovary is fading out and being replaced by a return to secretion of oestrone. Many theories have been put forward to explain these effects of prolactin. The effects may perhaps be determined in part by the state of the glands upon which the hormone acts, the corpus luteum, for instance, only secreting when it has reached a certain level of growth, under the action of the luteinizing hormone LH. If this fails, as gestation ends, the corpus luteum may lose its power to secrete, despite the continuing presence of LSH. Equally the mammary glands do not grow enough to be able to secrete until they have been stimulated by oestrone as well as progesterone, and this does not begin until the end of pregnancy is near. In this way, the action of prolactin might appear to be switched from one type of gland to the other at the time of parturition, but proof is lacking (Cowie and Folley, 1955). Such a situation would not necessitate a control of LSH different from that exerted by the brain over the other endocrinokinetic hormones; but what this is remains uncertain.

One view is that these hypophysial gonadotrophins and also ACTH and TSH (acting upon the adrenal cortex and the thyroid) depend for their stimulation upon one or more chemical substances that diffuse or circulate from the brain, rather than on nerve impulses; but the evidence relates chiefly to the morphogenetic effects of these hormones rather than to their endocrinokinetic actions. Recent experiments on rats have shown that if the adenohypophysis is removed from the brain and implanted in, say, the kidney, it undergoes partial degeneration in about 4 weeks, and ceases to secrete any of its hormones except LSH. By re-implanting it in contact with the median eminence of the brain, whence it originally came, the various cell types are induced to differentiate and regain much of their secretory capacity. The effect is first apparent on the growth-promoting fractions of ACTH and TSH (§ 4.221), and later upon the morphogenetic gonadotrophins, FSH and LH; there is also some slight evidence for the re-activation of the secretion-inducing action of TSH (§ 4.221). Re-implanting the adenohypophysial tissue in contact with other parts of the brain does not have this re-activating effect. Since there is no question of renewed nervous connection, it is claimed that the effect is due to a chemical cortical-releasing factor, *CRF*, from the median eminence of the brain (Nikitovitch-Winer and Everett, 1957). The substance is clearly not a true vascular hormone, since it does not act upon the hypophysis when the latter is out of contact with the brain, but supplied by the same blood. It may perhaps be a neurohormone (§ 1.2), or a short-lived vascular hormone, since some neurosecretory cells of the hypothalamus normally make contact with the portal blood supply of the adenohypophysis in the median eminence (Fig. 2-12). It is claimed that after re-implanting the hypophysis in contact with the median eminence, these cells may again pass their secretion for a short distance in the portal circulation, rather than just allowing it to diffuse between the hypothalamus and the hypophysis.

One curious result has been reported. Implantation of an adenohypophysis from a male rat, under the median eminence of a hypophysectomized female, is able to maintain her normal oestrus cycle, and even to support pregnancy. This must mean that the implanted hypophysis is secreting the luteinizing hormone, LH, the secretion of which is normally totally inhibited in the male (§ 4.232). It seems necessary to conclude that "the hypothalamus supplies not only a general stimulus to anterior pituitary function, but also *sets the pattern of this function*"* (Harris, 1955).

It would clearly be of interest if this type of experiment, and those on *CRF*, were to be related more specifically to effects upon the release of endocrinokinetic hormones from the hypophysis.

4.324 *Hormonal control of endocrine glands*

Four exceptional hormones, among those classed as kinetic, remain to be considered; they all come from the gonads and are therefore mesodermal in origin. Of these, the vertebrate gonads secrete three: OESTRONE and TESTOSTERONE, the two sex hormones which affect the tone and perhaps the activity of somatic muscle (§ 3.12), and PROGESTERONE, which is said to stimulate the secretion of oviducal glands in Amphibia and Mammalia (§ 4.12). Unlike any other kinetic hormones, the secretion of these vertebrate hormones is induced by endocrinokinetic hormones from the adenohypophysis (Table 17); such stimulation is characteristic of morphogenetic hormones, and it is noticeable that all the other activities of these hormones are morphogenetic (§ 4.232). Progesterone, in the course of preparing the uterus for the implantation of the embryo, causes growth of the uterine glands to the stage when secretion from them becomes possible; it may be that it does not actually stimulate the release of their secretion in the strict kinetic sense. The kinetic actions of oestrone and testosterone on somatic muscles may also be considered as incidental; they cannot in any case be claimed as the sole actions of these hormones. The last gonadial hormone in this group occurs in Gastropoda and controls the secretion of mucus from the oviduct as well as having far-reaching morphogenetic effects; it is, therefore, similar in function to progesterone, but nothing is known of the means whereby the secretion of the hormone is controlled.

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* My italics. P. M. J.

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CHAPTER 5

METABOLIC HORMONES

The term metabolic hormone is in general use, unlike the term kinetic introduced above; but some authors extend it to include morphogenetic hormones (Knowles and Carlisle, 1956). It is here applied to those hormones activating, inhibiting, or controlling the rate of certain biochemical processes of metabolic importance, occurring within the cells of the animal body, even when these processes can only be measured by their end-products, or by the accompanying changes in oxygen consumption. It is not used for those morphogenetic processes which, although they depend upon and are often limited by cell metabolism, yet manifest themselves in growth and differentiation.

Metabolic hormones in this limited sense differ sharply from kinetic hormones, because they do not act upon specific effectors or replace a type of control that is otherwise exerted by nerves. They control the rates of some cell activities which are often under no other apparent control, but appear to be determined genetically and to persist unaltered throughout the animal's life, at least until senescence intervenes. For instance, the absorptive activity of the gut cells of most animals seems to be as uncoordinated as the flagellar beat of sponge collar cells!

The hormones which introduce variability and control into some of these biochemical systems are further differentiated from kinetic hormones, at least among vertebrate examples, in that their secretion is not directly induced by nerves. In many cases the stimulus to secretion, apart from general nervous "stress", comes from an endocrinokinetic hormone (§ 4.2) intervening between the metabolic hormone and any possible nerve control. It follows that the action of these metabolic hormones is usually long-term in character, the most rapid probably being those concerned with water balance and response to stress. They will be considered in relation to their main actions, namely, the control of general metabolic rate and fat deposition (§ 5.1), intermediary metabolism of carbohydrates and protein (§ 5.2), and the balance of monovalent electrolytes and water (§ 5.3) and of calcium and phosphates (§ 5.4).

5.1 General metabolic rate

Changes in the general metabolic rate are reflected in the respiration rate of resting animals and also, less directly, in the deposition of fat, since the latter tends to increase with reduction in oxygen consumption (Table 18).

5.11 RESPIRATION

Hormones that increase respiration, and therefore increase oxygen consumption, are well-established in Insecta and Vertebrata; but are less clear in Crustacea. Hormones that decrease respiration are best known in Arthropoda.

5.111 *Increase in oxygen consumption*

Crustacea. Extracts of brain and nerve cord increase respiration in the freshwater crayfish, *Cambarus immunis.* Injection into eyestalkless crayfish of an extract of as little as one-tenth of a brain in 0·05 ml saline results in an increase of 22·8 per cent in oxygen consumption (Scudamore, 1947). This increase is in addition to that produced in the test animals by eyestalk removal (§ 5.12). Similar injections of an extract of the nerve cord and its ganglia can result in an increase of 29 per cent. Cautery of the eyestumps of eyestalkless crayfish, causing injury or stimulation of the brain, also produces a temporary increase of 56·8 per cent in oxygen consumption.

Insecta. The corpus allatum secretes a hormone which significantly increases the respiratory rate of insects.

A series of experiments by E. Thomsen (1949, and Thomsen and Hamburger, 1955) on the blowfly, *Calliphora*, are noteworthy for the use of extensive controls. Uniformity of material was maintained by using only 7-day-old adults cultured at 25 °C and starved for 24 hr before the males and females were tested separately. Since allatectomy, or removal of the corpus allatum,

TABLE 18. METABOLIC HORMONES CONTROLLING RESPIRATION AND FATS

EFFECT		VERTEBRATE		INVERTEBRATE	
		HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
5.11	RESPIRATION				
5.111	*Increase in O_2 consumption*	Thyroxine	Teleosts Amphibia Reptiles ? Birds Mammals	Brain Corpus allatum	*Cambarus* Diptera
5.112	*Decrease in O_2 consumption*	ACH (Hydrocortisone)	*Rana* Mammals (hibernating)	Ganglionic-X-organ and sinus gland	Decapod Crustacea
		—	—	Suboesophageal ganglion	*Bombyx* (diapause)
5.12	FAT METABOLISM				
5.121	*Increase in fat consumption*	Thyroxine	Mammals	Corpus allatum	All insect fat bodies, with storage in ovary (except *Carausius* and *Bombyx*)
5.122	*Decrease in fat consumption*	—	—	Sinus gland	*Hemigrapsus*

results in failure of ovarian growth (Part II, § 4), castrated females were also compared with mock castrated females, in which the abdomen was opened and the viscera were disturbed but the ovaries were left intact. The oxygen consumption of these controls, expressed in relation to live weight, showed no significant difference between either the normal males and females or the castrated and mock castrated females. In each group, estimations of oxygen consumption were made at 25 °C on about 60 unanaesthetized flies, tested individually every 10 min over a period of 2 hr.

The mean uptake of oxygen for all readings was expressed as mm^3 O_2/100 mg fly/10 min for each fly. The results were graphed (Figs. 5-1 and 5-2) to show the percentage of the total test group having their mean value within each range or class interval; they were also tested statistically for significance. Only a few results were rejected on the grounds that the flies were abnormally active during the experiment and depleted the oxygen supply.

To test the effect of allatectomy, the corpus allatum was removed from about 150 flies within 7½ hr of emergence from the pupa. The completeness of the operation was checked 7 days later, at the end of the experiment, by examining the ovaries. If these showed any appreciable growth due to corpus allatum stimulation, results from that fly were rejected.

In severity and duration, the control operation for allatectomy was, as nearly as possible, the same as the real operation, without actually damaging the corpus in any way. Mock-operated controls, compared with normal females, showed that the operation caused a drop in oxygen consumption, from $28{\cdot}3 \pm 0{\cdot}9$ to $27{\cdot}9 \pm 0{\cdot}9$ mm^3 O_2/100 mg/10 min; but removal of the corpus allatum reduced the mean for the three lowest values to $21{\cdot}3 \pm 0{\cdot}9$ mm^3 (Fig. 5-1). Taking all values (25 out of 26 flies) into consideration, the drop in oxygen consumption following removal of the corpus allatum amounted to 16 per cent; this is statistically significant (Thomsen and Hamburger, 1955).

Re-implanting corpora allata from other flies of similar age and sex into allatectomized flies was too severe an operation; but implantation of 3 corpora into normal females was carried out. These flies were compared with otherwise normal controls into which tissue other than corpus allatum was implanted. Survival was reasonable, although these mock-implanted controls showed a greater drop in oxygen consumption than those with mock allatectomy. The flies with implanted corpora allata had a mean oxygen consumption 19 per cent above that of the controls (Fig. 5-2). The corpus

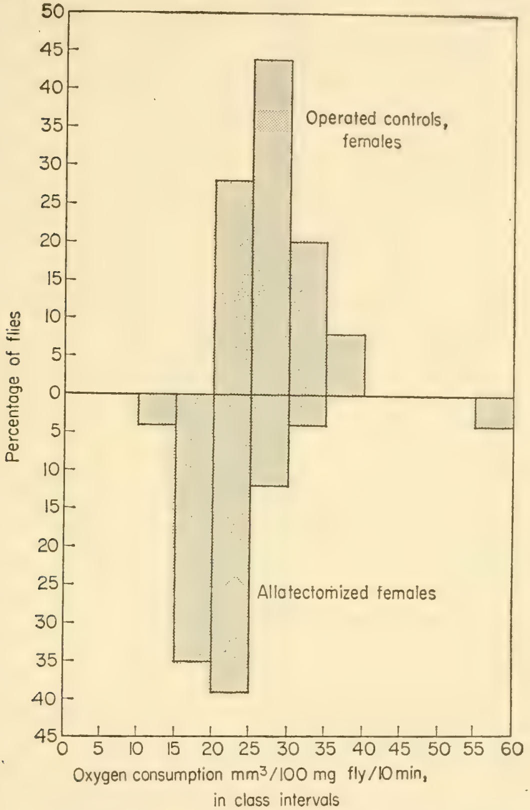

FIG. 5-1. Effect of removing the CORPUS ALLATUM on the oxygen consumption of 7-day-old blow-flies, *Calliphora erythrocephala*, at 25 °C. Oxygen consumption of allatectomized flies is shown below and that of mock-operated controls above. The number of flies giving results within each 5 mm^{3}O$_2$/100 mg fly/10 min class (abscissae) is shown as a percentage, up or down the ordinate scale. The mean oxygen consumption for the allatectomized flies is clearly reduced as compared with that of the controls (from Thomsen, 1949).

allatum in *Calliphora*, therefore, helps to maintain a high level of metabolism, as shown by oxygen consumption; and this is due to a secretion from the gland, since a significant positive effect is produced when glands with no nervous connection are implanted in the body cavity. Although it is now known that an active extract of the corpora allata can be obtained with ether, it has not yet been tested for its action on respiration (Hasegawa, 1957).

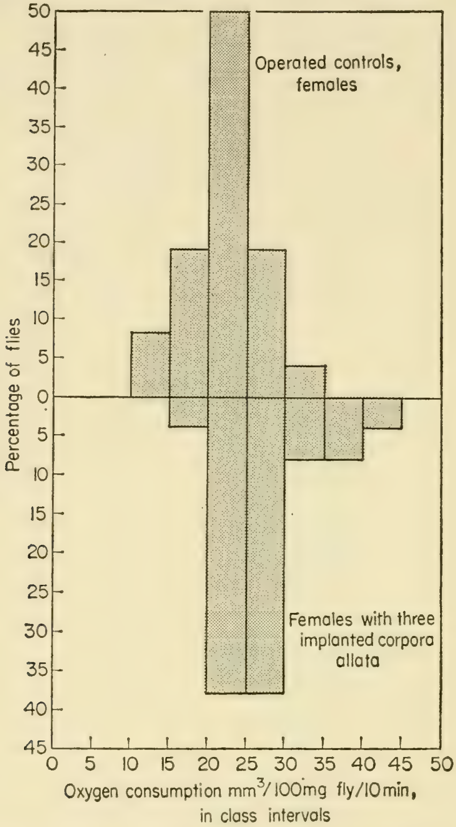

FIG. 5-2. Diagram, similar to Fig. 5-1, to show the effect of implanting three extra CORPORA ALLATA into *Calliphora*. The mean oxygen consumption for the flies with implanted corpora allata (below) is increased as compared with that of the mock-operated controls (above). (From Thomsen, 1949).

It is possible that the effect measured here should be associated with the diabetogenic action of the corpora allata (§ 5.211).

The action of the corpus allatum that increases oxygen consumption is not stimulated by nerves; nor is there any definite evidence of an endocrinokinetic effect (§ 4.213) upon them from either the median or lateral cerebral neurosecretory cells or their storage organ, the corpus cardiacum (E. Thomsen, 1952).

CHORDATA. Thyroxine secreted by the thyroid gland (§ 2.221) is the hormone that is effective in many chordates in raising the basal metabolic rate and increasing oxygen consumption; but it is best known in birds and mammals. The hormone contains iodine, and is not highly specific, since extracts from the thyroid glands of dogfish, *Scyliorhinus*, have almost the same effect upon mammals as do extracts of their own glands (Fig. 5-3). Although thyroxine is obtainable from many of the cold-blooded vertebrates, it is not always clear that it has any physiological function in them, or has at best more than seasonal significance in regard to metabolic rate. In many cases thyroxine acts mainly as a morphogenetic hormone (Part II, § 3).

PROTOCHORDATA. The Urochordata and Cephalochordata have a ciliated endostyle in the floor of the pharynx, the primary function of which is the secretion of mucus; but on embryological grounds the structure was, at one time, believed to be homologous with the thyroid of vertebrates.

UROCHORDATA. The ascidian, *Perophora*, has been examined to see if any of the tissues would accumulate radioactive iodine, as the thyroid gland does. This examination gave the anomalous result that the endostyle did not accumulate iodine, although the stolon did so (Gorbman, 1941).

CEPHALOCHORDATA. Unlike the ascidians, the amphioxus, *Branchiostoma*, does accumulate quite appreciable quantities of iodine in the endostyle (Thomas, 1956), but this is associated with mucopolysaccharides, and not with glycoproteins, as it is in thyroid glands. There is no evidence of any action of the iodine compound upon the amphioxus itself, though extracts provide iodine that can be utilized by the thyroid glands of Amphibia (Barrington, 1958).

AGNATHA. Lampreys undergo a well-defined metamorphosis from a larval ammocoete, which has a pharyngeal endostyle resembling that of the Protochordata, to an adult form with a thyroid comparable with that of other vertebrates. The endostyle of ammocoetes is capable of accumulating and storing iodine, associated with a glycoprotein, but the organ does not secrete the colloid, typical of a thyroid gland, until the adult stage. Leach (1946) found no evidence of changes in oxygen consumption accompanying these secretory changes; but he did not remove the gland nor try the action of extracts.

ELASMOBRANCHII. Dogfish and skates have well-defined thyroid glands, which can be removed relatively easily. Extracts of thyroid from the dogfish, *Scyliorhinus* (= *Scyllium*), increase the oxygen consumption of mammals (Fig. 5-3); but the presence of thyroxine in the blood of these fish seems to have no discernible effect upon their own metabolism. For a period of 42 days after thyroidectomy, the fish showed no appreciable changes in their oxygen consumption, as compared with mock-operated controls (Matty, 1954).

TELEOSTEI. Most teleost fish have diffuse thyroid tissue which is recognizable histologically, but almost impossible to remove surgically, except from the parrot-fish, *Pseudoscarus*, in which the gland is in a compact capsule. Like the thyroxine of elasmobranchs, that of teleosts is active in mammals (Fig. 5-4; D. C. Smith and Brown, 1952).

Earlier reports claim that the bony fish are as insensitive to the metabolic effects of thyroxine as the foregoing groups, at least when the thyroxine is of mammalian origin (Root and Etkin, 1937). More recently a slight increase in oxygen consumption has been induced in *Bathystoma*, by injecting extracts of THYROID from another teleost fish, *Pseudoscarus* (Smith and Matthews, 1948). It has also been found that synthetic thyroxine and thyroid stimulation by a thyrotrophic preparation (§ 4.221) both increase the oxygen consumption of goldfish, *Cyprinus*, by as much as 100 per cent for as long as 5 hr (Müller, 1953). Despite the well-known sensitivity of fish to handling, which makes experimentation extremely difficult (Hoar, 1957), control fish showed only 20 per cent increase in oxygen consumption, lasting only 40 min, as a result of saline injections.

AMPHIBIA. Seasonal changes in size and activity of the THYROID have been recorded for several amphibia (as well as for some fish and lizards) living in temperate climates (Lynn and Wachowski, 1951). It would seem as if the increase in thyroid activity in the summer enables these cold-blooded species to attain a high enough rate of basal metabolism even in temperate climes to become active despite the relatively low and variable temperature.

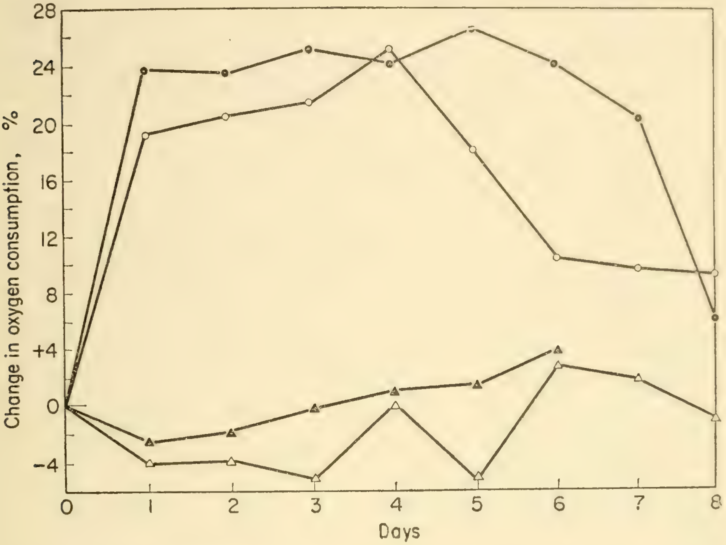

FIG. 5-3. Percentage changes in oxygen consumption of the rat, *Rattus*, (ordinates) with time in days (abscissae) when THYROID EXTRACTS are injected intra-peritoneally. There is little difference in effect between injection of 100 mg mammalian thyroid powder (black circles) and of 95 mg dogfish, *Scyliorhinus*, thyroid (white circles). Both cause considerable increase for about a week as compared with either normal controls (white triangles) or even controls injected with 2·0 ml 0·9% NaCl (black triangles). (From Matty, 1954).

Increase in oxygen consumption due to THYROXINE is never very great in Amphibia. Tadpoles and axolotls seem to be more responsive than adult frogs to thyroid treatment, whether this is given by feeding or injection. Thyroidectomy might make the frogs more sensitive, especially if they were tested in the winter with amphibian rather than mammalian thyroid extracts. The fact that increased respiration can also be obtained in adult salamanders by thyroid injection (Taylor, 1939) shows that the action is not merely a reflection of the stimulus towards metamorphosis in the larval forms (cf. Part II, § 3), as might otherwise be supposed.

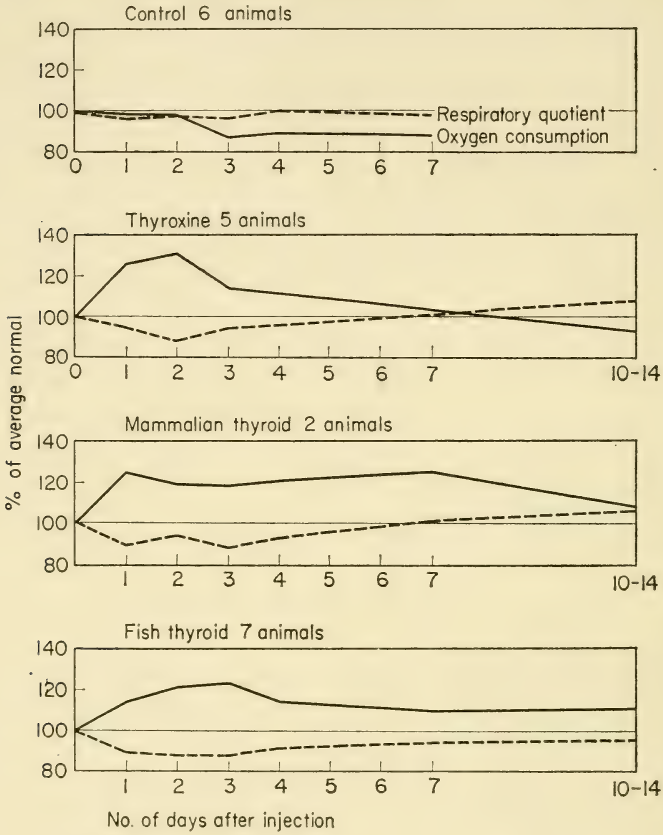

FIG. 5-4. Effects of thyroxine and thyroid extracts on the oxygen consumption (full line) and respiratory quotient (as percentages of the average values for the controls, shown by broken line) in male white rats, *Rattus*. Time in days as abscissae. The effects of purified thyroxine and the extract of a mammalian thyroid are similar. The extract of parrot fish, *Pseudoscarus*, thyroid causes less increase in oxygen consumption, but the effect lasts longer than the others (from D. C. Smith and Brown, 1952).

Aves. Judging by their high normal temperature of 39 °C (as compared with about 37 °C in man), the basal metabolism and heat output of birds must be the highest of any vertebrates. Yet evidence for the control of heat production and oxygen consumption by the thyroid is scanty. The basal metabolic rate drops by 20 per cent in pigeons within a week of thyroidectomy (Marvin and Smith, 1943). Heat output and respiration have also been shown to vary in different races of pigeons, and this is believed to be due to genetic variations in the activity, but not necessarily in the size, of their THYROID GLANDS (Riddle, 1947).

Mammalia. Hormone control of oxygen consumption is well-established in mammals, marked increase accompanying hyper-function of the THYROID GLAND or injection of THYROXINE (Fig. 5-3). A small injection of saline gives control evidence that the increase in oxygen uptake by the rat, due to the experimental procedure, is barely significant and of a different order of magnitude from the increase due to thyroxine of whatever origin (Matty, 1954); the converse effect, of thyroid removal, is not shown in the figure.

An important feature of the results is the close similarity in effect produced by injections of roughly similar amounts of thyroid extract from a mammal and from an elasmobranch or a teleost fish (Fig. 5-4).

There has been much discussion as to the exact rôle of thyroxine in mammalian metabolism, for measurements of its effect upon oxygen consumption only show the end stage in what may be a long chain of events, any or all of which may be sensitive to the hormone. Although thyroxine has been shown to act upon a very large number of enzyme systems in the body, the only consistent reaction that has been demonstrated *in vitro* is the effect of thyroxine in increasing the phosphorus turnover in oxidative phosphorylation (§ 5.211; Rawson *et al.*, 1955).

In vertebrates the thyroid gland is apparently always under endocrinokinetic control by THYROTROPHIN, TSH, from the adenohypophysis. In goldfish, *Cyprinus* (Müller, 1953), as well as in mammals, there is now definite evidence that secretion of the thyroid gland in relation to its metabolic action is stimulated by thyrotrophin, when this is injected as a purified extract (§ 4.221). This will probably be found to occur in all vertebrates.

5.112 *Decrease in oxygen consumption*

Crustacea. One of the hormones from the ganglionic-X-organ/sinus gland complex in the eyestalk of decapod crustaceans decreases oxygen consumption. This may either be a direct action or the hormone may inhibit the secretion, or action, of the brain hormone which increases oxygen consumption (§ 5.111); but no decision between these alternatives is possible at present.

The experimental evidence is not very satisfactory in the case of individual species; but taken together the results are consistent for all except *Leander*.

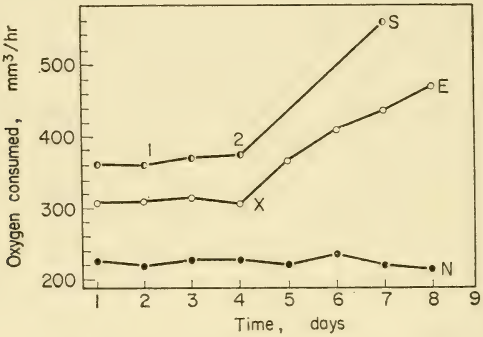

Fig. 5-5. Effect of eyestalk removal on the rate of oxygen consumption in the crayfish, *Cambarus immunis*. *N*, average for six normal crayfish; *E*, average for six crayfish from which both eyestalks were removed at *X* (there is no explanation of the high value for the previous 4 days); *S*, results for one crayfish from which removal of one eyestalk at 2 days gave no effect, but removal of the second at 4 days caused a marked increase in the one subsequent measurement. It is claimed that the eyestalks supply a respiration-inhibiting hormone (from Scudamore, 1947).

In *Cambarus immunis* there is no significant change in oxygen consumption after the removal of only one eyestalk, and very little after removing both sinus glands; but removal of both eyestalks allows the oxygen consumption to increase by about 60 per cent (Scudamore, 1947). Extract of sinus glands alone, injected into eyestalkless animals, is said to decrease oxygen consumption by

16 per cent; but when the glands are stored for some time before making alcoholic extracts, it is doubtful whether the extracts contain a substance that is normally released into the blood (Edwards, 1950). Control injections of saline and of muscle extracts did give negative results; but extracts of other parts of the eyestalk or even of whole eyestalks were not tested in this case (Fig. 5-5).

When such extracts are made and injected into eyestalkless crabs, such as *Uca*, oxygen consumption is reduced to nearly normal (Fig. 5-6).

Removal of sinus glands from *Astacus* (Frost *et al.*, 1951) has practically the same effect as a mock operation in which the glands are exposed but not removed, whereas removal of the whole eyestalk has a much greater effect (Table 19). This last experiment was not well controlled, but in *Cambarus* the removal of both antennae, which would be an operation of comparable severity to eyestalk removal, had no effect upon oxygen consumption.

TABLE 19. CHANGES IN OXYGEN CONSUMPTION IN *ASTACUS*, FOLLOWING SINUS GLAND OR EYESTALK REMOVAL

Individual values for oxygen consumption in cm^3/hr/100g body weight (from FROST *et al.* 1951).

SPECIMEN	A	B	C	D
Pre-operative values	3·06	4·56	4·77	5·57
After mock operation	——	5·13	5·33	6·17
After sinus gland removal	3·02	——	5·38	6·26
After eyestalk removal	5·16	——	——	7·77

Bliss (1953) interprets similar but more detailed experiments to mean that although the RESPIRATION-INHIBITING HORMONE is stored in the SINUS GLAND, and can therefore be supplied by injected extracts, its source is in the GANGLIONIC-X-ORGAN, which supplies sufficient hormone for control of respiration after removal of the sinus glands. Eventually, after removal of both sinus glands, which probably regulate the release of hormone into the blood, the crab, *Gecarcinus lateralis*, loses "its normal ability to vary the type and rate of metabolism". Indications of this are seen in a

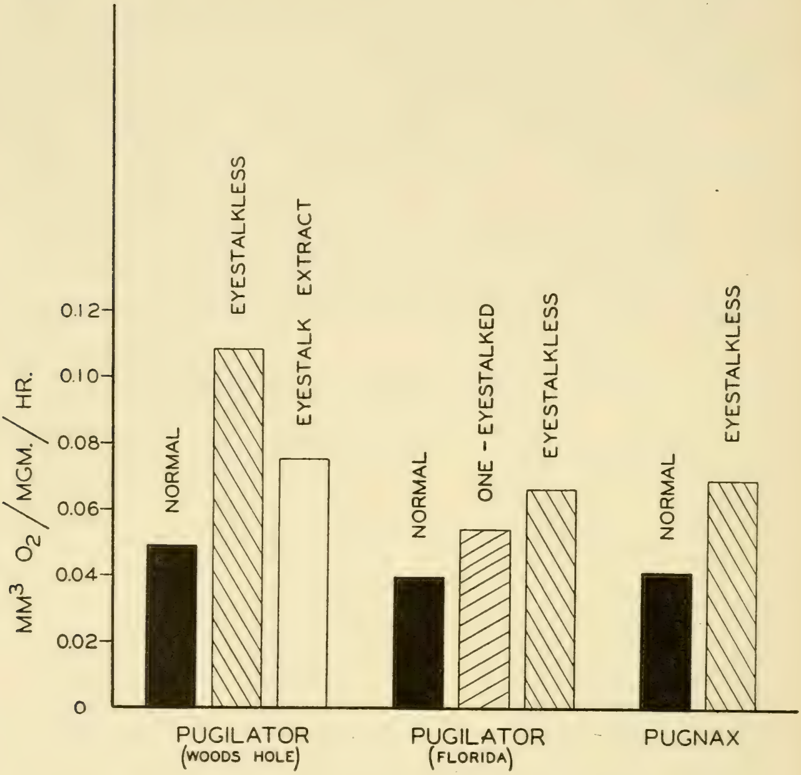

FIG. 5-6. Effects of eyestalk removal and subsequent injection of eyestalk extract on the average rate of daytime oxygen consumption of two fiddler crabs, *Uca pugilator* and *U. pugnax*, over a period of some weeks after treatment. Removal of one eyestalk removes less of the RESPIRATION-INHIBITING HORMONE than does that of two; the injected extract is not strong enough fully to replace it (from Edwards, 1950).

normal respiratory quotient and a low and relatively invariable respiratory rate, compared with normal crabs (Fig. 5-7*b*). The greatest increases in oxygen consumption in eyestalkless crabs are associated with the onset of moulting, which follows eyestalk removal (Part II, § 3) and tends to obscure other effects.

At Naples, *Leander serratus* shows no increase in oxygen consumption after eyestalk removal, neither does this operation lead to moulting, as in the other decapods so far considered (Scheer and Scheer, 1954). Nevertheless, successive stages in moulting are associated with changes in respiratory rate, and the writers postulate control by two or three hormones acting in turn; but these have not been located. A further counterclaim that the oxygen consumption of muscle homogenates from a number of Crustacea could be decreased by removing the eyestalks of the specimens shortly before taking the muscle samples seems to be unfounded (Scheer *et al.*, 1952).

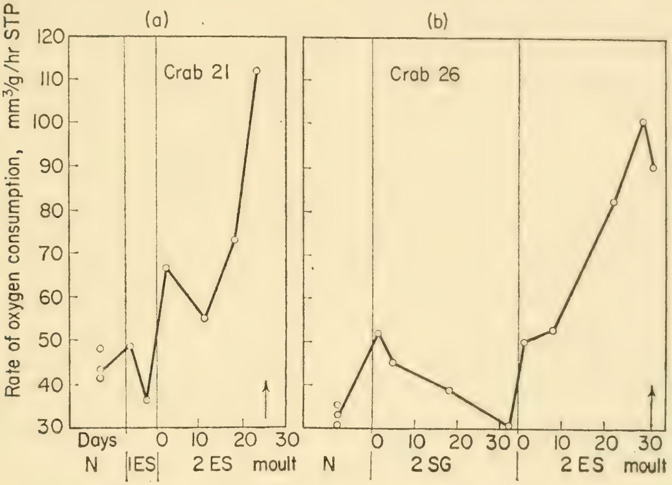

FIG. 5-7. Effects of eyestalk and sinus gland removal on the oxygen consumption of land crabs, *Gecarcinus lateralis*, at 10-day intervals after the treatments indicated. *a* and *b* show results from two different crabs; *N*, when normal; 1 *ES*, after removal of one, and 2 *ES*, after removal of two, eyestalks; 2 *SG*, after removal of two sinus glands only; arrows mark the time of ecdysis, or moulting, preparation for which must have occupied several previous days during which there is a great increase in oxygen consumption (from Bliss, 1953).

INSECTA. A marked decrease in respiration accompanies the phenomenon of diapause, or arrested development and inertia, which occurs seasonally in many insects. During diapause the cytochrome *c* system in the cells becomes inactive, except in some muscles, and the cyanide-stable respiration accounts for most of the remaining low rate of oxygen consumption. The phenomenon is best known in the embryos of the Japanese silkworm, *Bombyx*, (Fukuda, 1952 and 1953) and in the pupae of the Cecropia silkworm of America, *Hyalophora* (= *Platysamia*, Williams, 1952). There is a certain amount of disagreement as to whether the hormonal control is the same in both cases (Hinton, 1953) or different (e.g. Lees, 1955).

The action of a DIAPAUSE HORMONE, D, secreted by the SUB-OESOPHAGEAL GANGLION and reducing the oxygen consumption, is most clearly established in *Bombyx*. The situation is peculiar, as compared with other examples of hormonal control, in that secretion of the hormone D is determined by environmental factors in one generation, but only takes effect upon the next. It appears that the hormone secreted into the haemolymph of the female moth passes into her ovary, where sufficient D is absorbed into the eggs to put the resulting embryos into diapause within 28 hr of their being laid. The eggs containing the hormone can be recognized by their brown colour and are referred to as diapause eggs. They can be made to continue their development beyond the 28 hr by being put into Ringer solution after being stripped of their enclosing chorion and cuticle. It seems probable that this treatment allows the diapause hormone D to diffuse out of the embryonic tissues.

Some races of *Bombyx* have only two generations in the year. That which develops during the long, hot days of summer lays diapause eggs, which then over-winter in a dormant state. When the embryos begin to develop in the short, cool days of spring, they are not affected by sufficient daylight to induce the later secretion of D. So they lays eggs which develop directly, without diapause, during the summer, and the cycle starts again. Long daylength has been found to be the most effective environmental factor in determining the summer generation of these *Bombyx* to lay diapause eggs. It acts most strongly on the females just after the 18-somite stage in their development; but the effect is delayed until the adult stage, when the diapause hormone, D, is secreted. Other (univoltine) races of *Bombyx* have only one generation per year, and this always undergoes diapause, unless the source of D in the suboesophageal glands is removed at the pupal stage (Fukuda, 1953).

Much experimental work in Japan has proved that the source of the diapause hormone is in the suboesophageal ganglion of the adult, and that the brain can inhibit its secretion if the circum-oesophageal connectives remain intact. It is possible that the brain may even stimulate secretion of D, after the moth has been influenced by long daylength to lay diapause eggs (Fukuda, 1953). The following series of experiments are typical:

(1) If the suboesophageal ganglia are removed from late larvae after they have been exposed to long summer days (which normally induce the laying of diapause eggs) all the resulting females lay eggs which will not diapause, owing to the lack of D.

(2) If the brain is removed at pupation from specimens that have been exposed as embryos to short spring days (which should result in their all laying non-diapause eggs) they turn into moths of which only 14 per cent lay such eggs, while 36 per cent lay diapause eggs, and the rest lay mixed batches. The increase in diapause eggs is interpreted as being due to removal of the inhibiting action of the brain, which leaves the suboesophageal ganglia free to secrete D. It may also show the lack of sufficient stimulus to cause all the females to lay only diapause eggs.

(3) If isolated abdomens of specimens that should lay non-diapause eggs are used as hosts, the type of eggs actually formed in them can be influenced by transplants, as follows:

(a) Brain or prothoracic gland transplanted alone has no effect.

(b) Brain and suboesophageal ganglia, joined by their connectives, have no effect if taken from a moth which has been climatically determined to lay non-diapause eggs, and in which the brain was therefore inhibiting the secretion of D.

(c) Suboesophageal ganglia transplanted alone, or severed from the brain and therefore not inhibited by it, result in the laying

> of diapause eggs in 70 per cent of cases. This effect can, in fact, be produced by ganglia from males as well as females, and even from moths of other species, including *Antheraea pernyi* (which does not itself lay diapause eggs but has a so-called "pupal diapause"; Lees, 1955).

These experiments have been substantiated by extraction of pure diapause hormone from the suboesophageal ganglia of *Bombyx* (Hasegawa, 1957).

Another very unusual feature has been postulated for the hormones concerned with diapause in *Bombyx* (Hinton, 1953). Since the adults are apparently unaffected by the diapause hormone which they secrete, and the eggs they lay continue to develop for over a day before the hormone D acts upon them, it is suggested that the MOULT-PROMOTING HORMONE, ECDYSONE (Part II, § 3), from the prothoracic glands, in some way protects the tissues of the adults from the action of the diapause hormone, present at the same time. Moreover, some ecdysone must be passed into the eggs with D before they are laid, and this postpones the onset of diapause. It is assumed that ecdysone is broken down in a few hours in the young embryo, whereas the break-down of D is extremely slow, so that diapause lasts until the following spring when the supply of D is eventually eliminated. This might also be true for the embryos of *Locustana pardalina*, in which diapause ends and growth begins again before any organized endocrine glands have developed (Jones, 1956).

In the Cecropia silkworm, *Hyalophora*, the climatic determination of diapause acts on the late embryo or early larva, which, unlike that of *Bombyx*, itself undergoes diapause some months later in the pupal stage, when the suboesophageal ganglion is already well developed. Hinton (1953) maintains that the hormone D is again responsible for causing diapause; but others, especially Williams (1952), claim that it is due to the lack of the PROTHORACIC HORMONE, rather than to the presence of an inhibitor, D, acting on the brain. The somewhat scanty evidence can be interpreted either way. It is agreed that the end of diapause is due to the re-activation of the prothoracic glands. This is due to renewed neurosecretion of PROTHORACOTROPHIN from the brain (§ 4.211), as in moulting; it can be induced artificially by chilling the brain. Injection of extracts of prothoracic gland can also break diapause. Even if D is the cause of diapause here, it is still not known whether the action of the prothoracic hormone in bringing diapause to an end is to inhibit the further secretion of D, or to release the tissues from its action, as in the adult *Bombyx*.

The fact that the diapause of hosts and their parasites is normally synchronous provides further evidence that diapause is determined hormonally (Hinton, 1957). For instance, an ichneumon, *Diplazon fissorius*, parasitizes several species of syrphids, although some of them diapause and others do not. If an active parasite is transplanted (Schneider, 1950) from an active host to one that is diapausing, the parasite becomes immobile; but in the reciprocal case, when the diapausing parasite is transplanted from a diapausing larval host to an active pupal host, the parasite resumes active growth. It therefore seems that the hormones of the host are able, not only to control the metabolic level of its own tissues, but also to override those of the parasite.

VERTEBRATA. There is not much conclusive evidence for hormones that decrease oxygen consumption in vertebrates, except in amphibians and possibly mammals.

AMPHIBIA. A significant decrease in oxygen consumption, of about 30 per cent, occurs in starved frogs in the 4th and 5th weeks of treatment with A.C.E., an extract of the ADRENAL CORTEX, if 0·36 ml/Kg body weight is injected on alternate days (Calhoon and Angerer, 1955). There is no difference in loss of body weight during this period as between injected frogs and untreated controls. The authors do not specify which cortical steroid is dominant in Upjohn's extract which they used. It might be expected that one of those concerned with carbohydrate metabolism, rather than one of the "mineralocorticoids", would decrease oxygen consumption.

MAMMALIA. Decrease of basal metabolic rate and of oxygen consumption occurs chiefly in hibernating mammals; at other times the possible need for a hormone having this action would seem to be confined to maintaining the normal equilibrium in opposition to the thyroid (§ 5.111). There has been much work on the effect of injecting extracts of adrenal cortex into mammals;

but the results reported have been contradictory. It is probable that in physiological doses the cortical hormones cause no significant change in the oxygen consumption of normal mammals.

In hibernation the presence of active ADRENAL CORTEX seems to be essential, in conjunction with relatively inactive thyroid glands. It is therefore possible that cortical secretion helps to reduce oxygen consumption in hibernating mammals, as it does in normal frogs; but the adrenal cortex is by no means the sole cause of all the changes in metabolism and heat regulation that occur in hibernation (Lyman and Chatfield, 1955).

5.12 FAT METABOLISM

Changes in fat stores in the body, like changes in respiration, are often indicative of the general rate of metabolism, so that increased fat consumption and decreased storage may accompany increased oxygen consumption, and may be controlled by the same hormone. Periodic changes in activity, such as moulting, may be preceded by an increase in the rate of fat consumption, and others, such as hibernation, by an increase in fat storage.

5.121 *Increase in fat consumption or decrease in storage*

CRUSTACEA. Fat consumption increases after the removal of a moult-inhibiting factor in the sinus gland (§ 5.122); but, as yet, no hormone or extract has been found that stimulates fat consumption. It might be sought in the brain, which yields an extract that stimulates respiration (§ 5.111).

INSECTA. The presence of the CORPORA ALLATA, with their stimulating effect on the metabolic rate, tends to reduce the store of fat in the fat bodies of most insects; in adult females, when yolk is being deposited in the ripening eggs, the corpora also facilitate transport of fat to the ovary. This occurs in all insects except in *Bombyx*, where the eggs are matured before the adult emerges, and in *Carausius*.

A detailed study of the production and transport of fat in the grasshopper, *Melanoplus differentialis*, shows that the corpora allata cause a change in metabolism in normal females, from an early phase of fat accumulation in the fat body, to a later phase when the fat body becomes depleted and all the fat is passed into the egg yolk (Pfeiffer, 1945). If the corpora allata are removed near the beginning of the adult stage (whether the ovaries are present or not), the fatty acid content of the fat bodies continues to rise at the same rate as before. If adult females retain their corpora allata, the usual depletion of the fat bodies follows, even in castrated specimens, showing that the ovary has no effect. Normally the corpora allata begin to secrete sufficiently to cause this change some time after the emergence of the adult, as they are inhibited during metamorphosis (Part II, § 3).

VERTEBRATA. THYROXINE causes decrease in fat stores, at least in mammals. Treatment of rats with thyroxine causes an increase in the synthesis and turnover of phospholipids in the liver and in the secretion of cholesterol in the bile (Rawson *et al.*, 1955). Conversely, hypofunction, or reduction, of the thyroid is accompanied by increase in fat deposition, provided the food supply is not limited. The secretion of the thyroid is stimulated by THYROTROPHIN from the hypophysis (§ 4.221).

5.122 *Decrease in fat consumption or increase in storage*

CRUSTACEA. A SINUS GLAND HORMONE seems to help in maintaining the amount of fat stored in the body. When the sinus gland or the whole eyestalk is removed, there is a rapid disappearance of fat, as well as an increase in oxygen consumption (§ 5.111), followed by the onset of moulting. It is not known if the same hormone controls all three processes.

The effects of starvation, with and without sinus gland removal, have been examined in the crab, *Hemigrapsus nudus*. The sinus glands were removed by drilling through the eyestalk and aspirating out the gland tissue. Male and female crabs were compared with normal controls in the same inter-moult stage, but no figures are given for mock-operated animals. Female crabs normally have more fat than males, and 23 days of starvation makes no significant difference; but sinus gland removal, followed by starvation for 23 days, results in the fat content dropping by nearly a half in both sexes (Table 20).

TABLE 20. CHANGES IN FAT CONTENT OF THE BODY OF CRABS (*HEMIGRAPSUS NUDUS*) FOLLOWING STARVATION AND SINUS GLAND REMOVAL

All values are given on a wet weight basis and are means of measurements on two to four individuals. The differences in fat, due to sex, and the losses after sinus gland removal are significant (from Neiland and Scheer, 1953).

	NORMAL		STARVED 23 DAYS		STARVED WITH SINUS GLAND REMOVED	
Sex	M	F	M	F	M	F
Body weight, g	10·5	9·3	9·5	7·4	10·3	7·4
Fat index/g	4·31	6·13	4·76	6·4	2·82	3·79

This, in conjunction with evidence on glycogen and chitin content (Table 23), suggests that "the eyestalk principle of crustaceans restrains . . . metabolism, but especially those processes connected with preparation for a molt" (Neiland and Scheer, 1953). But this finding is, perhaps, somewhat sweeping, since the authors appear only to have tested removal of the sinus glands, and not to have compared this with removal of the whole eyestalk, nor to have replaced either organ by injection of its extract. This is important, since the sinus glands are usually only storage organs for neurosecretory cells in the brain or the ganglionic-X-organ, both of which were left intact in these experiments and might have been expected to continue to supply some of the fat-preserving hormone as well as of the moult-inhibiting hormone. It has already been noted that the comparable hormone that restrains oxygen consumption is more abundant in the whole eyestalk than in the sinus glands alone (§ 5.112 and Fig. 5-7).

VERTEBRATA. No hormones have been specifically associated with fat storage in vertebrates, apart from lack of thyroxine (§ 5.121) or of thyrotrophin (§ 4.221). Relative inactivity of the thyroid seems to be the main factor in allowing accumulation of the fat stores that are necessary for hibernation in mammals (§ 5.112).

It has been claimed that, in the brown trout, *Salmo trutta*, most fat is deposited in the gut wall around midsummer, when the thyroid gland reaches the single peak of its activity, as estimated by its accumulation of radioactive iodine (Swift, 1955). This seems to be anomalous; but it may be noted that fat is also deposited in January, before the spring growth period. There may, therefore, be no causal connection between fat deposition and thyroxine secretion.

5.2 INTERMEDIARY METABOLISM OF CARBOHYDRATES AND PROTEINS

The biochemistry of intermediary metabolism is complex, but it need not be considered in detail here, since it is possible to measure the end-products of anabolism or catabolism, rather than the series of chemical transformations within these processes. These measurements can then be related to hormone treatment. Evidence is accumulating to show that in arthropods and in vertebrates the metabolism of carbohydrates and of proteins is often linked; but different hormones may be concerned in controlling the two types of metabolism, which will therefore be considered separately.

5.21 CARBOHYDRATE METABOLISM

Among the carbohydrates, sugars are most easily traced and can be measured quantitatively in the blood, as they increase in quantity after a meal, or after hormone treatment, and then decrease as they pass into the tissues to be stored or assimilated. Their distribution between the blood and the tissues is normally maintained at a relatively stable level by a balance of hormones, the diabetogenic type increasing the blood-sugars and the anti-diabetogenic decreasing them. Evidence of both types have been obtained in Arthropoda, as well as in Vertebrata (Table 21).

5.211 *Increase in blood-sugar by "diabetogenic" hormones*

CRUSTACEA. The SINUS GLAND is the main source of a diabetogenic hormone in both the crayfish, *Astacus*, and the blue crab, *Callinectes*. This has been shown in carefully controlled comparisons (Table 22) between the effects of "stress" caused by asphyxia in normal and in operated animals, from which either the whole eyestalk or the sinus gland alone had been removed (Kleinholz

TABLE 21. METABOLIC HORMONES CONTROLLING CARBOHYDRATES AND PROTEINS

	EFFECT	VERTEBRATE		INVERTEBRATE	
		HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
5.21	CARBOHYDRATES				
5.211	*Increase in blood-sugar* or "*Diabetogenic*"	ACH (hydrocortisone)	Amphibia *Columba* *Rattus*	Sinus gland	*Palaemon* *Astacus* *Callinectes* *Paratya* *Panulirus*
		Glucagon	*Thunnus* *Gallus* *Oryctolagus* *Canis* *Felis*		
		Adrenaline (emergency)	Mammals	C. allatum	*Carausius*
5.212	*Decrease in blood-sugar* or "*Antidiabetogenic*"	Insulin	Aves ? Mammals	Prothoracic gland	Insecta (at pupation)
5.22	PROTEINS				
5.221	*Restraint of protein catabolism*	—	—	Eyestalk (MIH ?)	*Hemigrapsus* *Carcinus*
5.222	*Increase in protein synthesis*	—	—	Y-Organ ? (MPH)	*Eriocheir* *Carcinus*
		—	—	Brain and C. cardiaca	*Periplaneta* *Melanoplus* *Calliphora*
		—	—	C. allatum	*Carausius*
5.223	*Decrease in protein synthesis or increase in protein catabolism*	ACH (Hydrocortisone)	Mammals	Eyestalk tip	*Carcinus*

et al., 1950). It is clear that an increase in blood-sugar, or hyperglycaemia, is produced in these crustaceans as a result of stress, very much as in mammals, as long as the sinus gland has its innervation intact; the converse experiment of injecting sinus gland extract raises the blood-sugar content as much as 400 per cent in *Callinectes* (Abramowitz *et al.*, 1944). The comparable effect of excitement or pain in inducing hyperglycaemia in *Callinectes* (but not in the less pugnacious *Astacus*) was shown by injecting plain saline; this produced as great a rise in blood-sugars as injections of adrenaline, but in either case the effect could be almost completely inhibited by cutting the nerve to the sinus gland.

Injection of an eyestalk extract, not identified more exactly, increases blood-sugars in a number of other Crustacea, including the freshwater shrimps, *Paratya* and *Palaemon* (Nagano, 1951). An eyestalk hormone also increases the concentration of glucose in the blood, and apparently decreases its utilization in the tissues of two species of spiny lobsters, *Panulirus* (Scheer and Scheer, 1951). However, since C^{14}, when used to label injected glucose, does not reappear in the respiratory CO_2 during the following 24 hr, but 30 per cent of it can eventually be recovered from the skeleton, it seems that glucose must be mainly concerned in chitin formation. It is therefore arguable that the hormone of the eyestalks which increases blood-sugars should not be considered as comparable with the diabetogenic hormones of vertebrates.

The hormone secreted from the sinus gland is presumably a neurosecretion derived as usual from either the brain or the ganglionic-X-organ; but the exact origin has not yet been decided. There appears to be direct nervous control of the release of the diabetogenic hormone, with no intervention of any endocrinokinetic hormone.

INSECTA. Reduction in blood-sugar follows the removal of the CORPORA ALLATA in the stick insect, *Carausius* (= *Dixippus*; L'Hélias, 1955), indicating a diabetogenic function for their secretion.

There appears to be no direct evidence of the corpora allata being controlled by a hormone from the brain in this case, any more than there is in relation to oxygen consumption.

VERTEBRATA. Recent information on diabetogenic hormones in

Table 22. The effect of asphyxia on the concentration of blood-sugar

The concentration of blood-sugar, before and after induced asphyxia, is given in mg/100 cm^3 blood (mg %), with the standard deviation from the average of the group; the numerals in parentheses following the concentration after asphyxia indicate the number of animals in the group that showed increases of less than 3 mg %; — ES, eyestalkless animals; — SG, sinus glandless animals; — SGN, animals in which both sinus glands had been denervated. Asphyxia for *Callinectes* was achieved by keeping the animals in air; for *Astacus* it was necessary to maintain them in de-aerated water. (From Kleinholz *et al.*, 1950).

ANIMALS		ASPHYXIA	AVERAGE MG % BLOOD-SUGAR		AVERAGE % INCREASE
CONDITION	NO. USED	DURATION IN HOURS	BEFORE	AFTER	
Astacus:					
Normal	10	1	16·7 ± 7·9	29·0 ± 21·1 (4)	74
— SG	9	1	14·3 ± 8·9	14·2 ± 8·7 (8)	0
Normal	16	3	18·3 ± 6·5	52·9 ± 22·4 (1)	189
— SG	10	3	11·6 ± 5·8	12·7 ± 5·1 (8)	9
Callinectes:					
Normal	4	2	9·2 ± 1·7	27·7 ± 10·3 (0)	201
— ES	6	2	9·7 ± 3·8	8·0 ± 3·2 (6)	0
— SGN	11	2	14·4 ± 4·9	16·9 ± 6·5 (6)	17

cold-blooded vertebrates and birds has shown that they resemble those in mammals. There are two different diabetogenic systems that can increase the blood-sugars in different species: either glucagon from the pancreas or a hormone from the adrenal cortex (Table 21).

TELEOSTEI. The tunny, *Thunnus germo*, and other fish secrete a substance like glucagon from the α cells of the pancreas, but the action of an extract has only been tested on rats (Mialhe, 1952).

AMPHIBIA. In frogs, *Rana*, the ADRENAL CORTEX probably plays a part in the control of the sugar balance by secreting a diabetogenic hormone; for adrenalectomy and the consequent lack of this hormone results in hypoglycaemia, or a low level of blood-sugar. Adrenalectomy is also said to reduce the frog's capacity to absorb glucose and galactose from the gut, and to cause loss of glycogen reserves from the liver (Chester Jones, 1957*a*). The first effect is due to the unopposed action of insulin, the presence of which has now been recorded in frogs. The last effect is probably indirect; for the hypoglycaemia induced by the insulin would in due course inhibit further insulin secretion and so prevent the building up of glycogen reserves, even if it would not cause their depletion (§ 5.212).

In Urodela the diabetogenic hormone is also cortical, but comes from the interrenal tissue.

REPTILIA. There is recent evidence for GLUCAGON being the diabetogenic hormone in some lizards (Miller and Wurster, 1959).

AVES. The total blood-sugars are normally about twice as high in birds as in mammals, and show a cyclical change, increasing by 14 per cent near the time of egg-laying. It is possible that, like mammals, different birds have different diabetogenic hormones. In the intact pigeon, *Columba*, injections of adrenocorticotrophin, ACTH, cause a great increase in blood-sugar, lasting about 10 hr. Pancreatectomy does not influence this reaction, but adrenalectomy eliminates it (Riddle *et al.*, 1947). This is the same as in the rat, where the ADRENAL CORTEX is the source of the main diabetogenic hormone. In the chick, on the other hand, blood-sugar can be raised by STH, the so-called growth hormone of the anterior pituitary (Hsieh, Wang and Blumenthal, 1952). This seems to be like the dog, where STH acts as an endocrinokinetic hormone stimulating the secretion of glucagon, the actual diabetogenic hormone, from the pancreas. No mention of glucagon has been made in relation to this work on the chick; but the pancreas of some other birds contains large amounts (Miller and Wurster, 1959).

Mammalia. A striking difference between different mammals occurs in respect of their diabetogenic hormones. In some carnivores, including the dog and cat, but not the ferret, the main hormone that increases the blood glucose is glucagon, secreted by α cells in the islets of Langerhans (§ 2.222). In the rat and in man, the main hormone having this action is hydrocortisone from the adrenal cortex. This has interesting repercussions in experimental work, since the cortex is stimulated by ACTH from the adenohypophysis (§ 4.231), and glucagon by the "growth" hormone, STH, from the same source (§ 4.222); it follows that

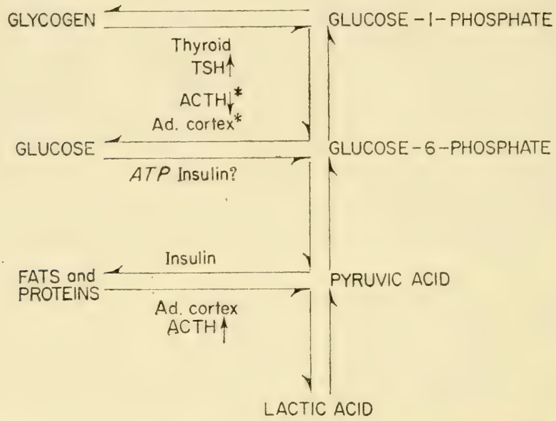
GLYCOGEN
GLUCOSE - I - PHOSPHATE
Thyroid
TSH↑
ACTH↓*
Ad. cortex*
GLUCOSE
GLUCOSE - 6 - PHOSPHATE
ATP Insulin?
Insulin
FATS and PROTEINS
PYRUVIC ACID
Ad. cortex
ACTH↑
LACTIC ACID

Fig. 5-8. Diagram to show some of the hormones believed to facilitate chemical transformations in the intermediary metabolism of the rat, *Rattus*. In the dog, *Canis*, and some other carnivores, the diabetogenic action of the adrenal cortex, Ad. cortex*, stimulated by ACTH*, is replaced by that of glucagon stimulated by STH. *ATP* is adenosine triphosphate, an enzyme and not a hormone (from Ebling, 1951, and Fieser and Fieser, 1950).

carnivores may become diabetic if treated with growth hormone, but that the rat can continue growing under the same treatment, with little disturbance of its sugar balance, except in extreme cases. Glucagon secretion can also be stimulated directly by a low content of sugar in the blood (cf. § 5.521; Saka, 1952).

The action of glucagon is usually estimated from its effect upon the glucose level in the blood; but it is claimed that the hydrocortisone acts at two stages in the process of gluconeogenesis; by stimulating the transformation of fats and proteins to pyruvic acid, and also by increasing the blood-glucose at the expense of glucose-6-phosphate in the tissues and liver. The transformation of glycogen stores to free glucose via phosphorylated glucose is facilitated by thyroxine (§ 5.111); but the latter hormone alone is not able to release glucose into the blood stream (Fig. 5-8).

As has been mentioned, hydrocortisone secretion is stimulated by the endocrinokinetic hormone ACTH, and glucagon by STH.

Adrenaline can also have a diabetogenic effect in liberating sugar from liver glycogen into the blood. This is presumably an indirect effect, since ADRENALINE causes a slow release of ACTH (§ 4.231). The latter must be the main cause of the hyperglycaemia associated with stress and excitement, and (like the comparable sinus gland reaction in *Callinectes*) is also under direct nervous stimulation.

5.212 *Decrease in blood-sugars by antidiabetogenic hormones*

ARTHROPODA. A hormone of this type has not so far been reported for the Crustacea.

INSECTA. It has long been postulated that an antidiabetogenic hormone is released just prior to moulting, and it is now believed to be the same as the MOULT-PROMOTING HORMONE, ECDYSONE, from the PROTHORACIC GLANDS, or their equivalent in the ring gland of *Calliphora* (Dennell, 1949). The secretion of the moulting hormone is under endocrinokinetic control from the neurosecretory cells of the INTERCEREBRUM.

VERTEBRATA. The main antidiabetogenic hormone of vertebrates is INSULIN, secreted from the β cells of the pancreatic ISLETS OF LANGERHANS (§ 2.222). This hormone lowers the level of sugars in the blood by facilitating the supply of glucose to the tissues; but there are two possible sites for this action. One is the cell membranes of the blood vessel walls and the tissues, where there is evidence that insulin stimulates the transfer of glucose from the blood stream to the tissue fluids. The other is the seat of chemical transformation within the tissues, where intracellular enzymes, particularly hexokinase, hasten the phosphorylation of glucose by adenosine triphosphate (*ATP*). This results in the formation of glucose-6-phosphate, which is the starting-point both for utilizing glucose and for converting it to glycogen (Fig. 5-8). It has recently been postulated (Levine and Goldstein, 1955*a*) that stimulation of the transfer system is the main action of insulin, and that it merely

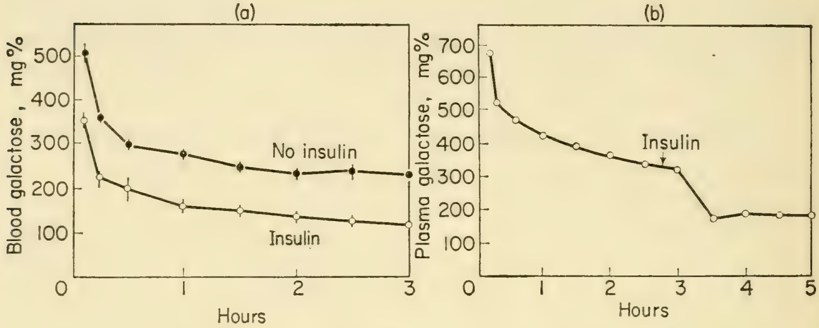

FIG. 5-9. Changes in distribution of injected galactose caused by INSULIN injection in eviscerated and nephrectomized dogs, *Canis*. Galactose was injected at the beginning at the rate of 1 g/Kg; ordinates show the amounts recovered in the blood in mg per 100 g (not %); abscissae show time in hours after the injection; vertical lines show the range of variation of all values in 6 or 8 specimens. (*a*) The upper curve shows that when equilibrium is reached after about 1 hour, in absence of insulin, the galactose concentration is such that it occupies 45% of the body weight, or the volume of the blood only. The lower curve, for similar measurements made in presence of insulin, shows that the galactose is distributed in a larger volume, amounting to 70% of the body weight and equivalent to all the body fluids. (*b*) A similar record in which insulin is added after equilibrium in the blood has been reached in 2½ hr and causes a drop to the 70% body weight distribution, as before (from Levine *et al.*, 1950).

allows of a more rapid movement of glucose both in and out of the cells. Since the cell membranes are not permeable to the phosphorylated hexose, the formation of this within the cell would automatically have the rôle of trapping the glucose and rendering the transfer virtually a one-way system. Even though insulin had no effect upon the rate of phosphorylation, such a system "would be consistent with the fact that glucose utilization [in contrast to galactose distribution, Fig. 5-9] is a summated phenomenon of both insulin-stimulated cellular entry and of metabolic disposal".

FISH. In some teleosts and elasmobranchs INSULIN maintains a relatively low level of sugar in the blood; but the results of pancreatectomy are inconsistent, presumably because the source of glucagon (§ 5.211) is removed as well as that of the insulin.

AMPHIBIA. In *Rana* and *Bufo* the loss of INSULIN by pancreatectomy results in hyperglycaemia, or increased blood-sugar, because the source of the diabetogenic hormone in the adrenal cortex is not removed (Houssay, 1959).

AVES. Injected INSULIN is effective in lowering the level of blood-sugar in pigeons, which can survive higher doses of this hormone than can mammals (Riddle *et al.*, 1947).

MAMMALIA. Experiments have been carried out on anaesthetized and eviscerated dogs and rats to test the effect of INSULIN on the level of blood-sugars, in the absence of utilization and storage in the liver or loss by excretion (Levine *et al.*, 1950). Glucose is steadily consumed in the tissues; but another monosaccharide, galactose, is not utilized. When a known quantity of the latter is injected, it is found to distribute itself in a volume equivalent to about 45 per cent of the animal's weight. This is equal to the volume of circulating blood. After injection of insulin the concentration of galactose in the blood drops, as though it were distributed in a volume equal to 70 per cent of the body weight (Fig. 5-9). This is equivalent to the volume of all the body water, and it is assumed, therefore, that the sugar has been allowed to pass into the intracellular fluid of the cells. By comparing a number of monosaccharides, it can be further shown that insulin only facilitates their passage into the tissues from the blood if the configuration of their molecules is such that the side-chains attached to the first three carbon atoms are the same as those of glucose. The optical isomers are unresponsive to insulin (Fig. 5-10). This suggests a point of further chemical attack upon the problem of the nature of the hormone action in lowering blood-sugars and making them available to the tissues; but the relation

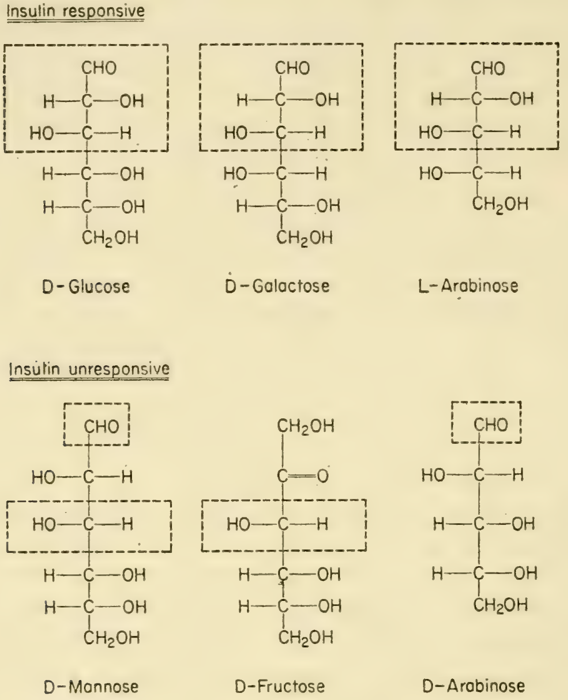
Insulin responsive
D-Glucose
D-Galactose
L-Arabinose
Insulin unresponsive
D-Mannose
D-Fructose
D-Arabinose

FIG. 5-10. The structure of some of the sugar molecules which have been found to be responsive to insulin and to resemble glucose in having the same side chains on the three terminal carbon atoms; and (below) three molecules of sugars which differ, however slightly, from glucose, and are found to be unresponsive to insulin (from Levine and Goldstein in Stetten and Bloom, 1955).

of these facts to the known chemical structure of the insulin, which is a protein, is not yet within sight.

The rate of secretion of insulin is self-regulating, in that a high level of blood-sugar increases insulin; and, as this lowers the level, so the insulin secretion itself is reduced.

There is no known hormone that stimulates the secretion of insulin, unless secretion is found to be related to the increased growth of the gland, which is said to occur as a result of injecting extracts of the posterior pituitary (Staszyc, 1956). This is as yet unconfirmed.

The claim that STH increases insulin secretion is based on an indirect effect, since it only occurs in those species where STH stimulates glucagon to raise the level of blood-sugars, and this in turn stimulates the insulin secretion (§§ 4.222 and 5.521).

5.22 PROTEIN METABOLISM

Hormones play a part in protein metabolism in Arthropoda and Vertebrata, but the results so far reported are not always clear. Noble (1955) points out that, in vertebrates, most attempts to assess nitrogen, which is a characteristic element in proteins, have been based on measurements of the over-all balance in the body, whereas a more realistic picture might be obtained by following reactions in different organs of the body separately. Increased protein catabolism in one organ may be accompanied by an increase in nitrogen excretion (§ 5.222), or it may be mainly responsible for supplying materials for protein anabolism in some other organ.

ARTHROPODA. The same difficulties of interpretation are probably true for Arthropoda. Perhaps the best that can be suggested at present is that an eyestalk hormone in Crustacea tends to restrain protein breakdown and nitrogen excretion and that the Y-organ hormone may inhibit them (Table 24). In Insecta a brain hormone appears to be associated with an actual increase in new protein formation. No hormones are yet known to stimulate catabolism in either Crustacea or Insecta.

5.221 *Restraint of protein catabolism*

CRUSTACEA. It has been claimed that an EYESTALK HORMONE restrains protein catabolism and that removal of the sinus gland, which is the main storage organ of the hormone, results in protein breakdown and loss of nitrogen; but the evidence is ambiguous, partly because the results seem to vary with stages in the moult and intermoult cycle.

Positive evidence shows that sinus gland removal causes a loss of nitrogen in the crab, *Hemigrapsus*. Sinus gland removal also leads eventually to moulting, because of the absence of the moult-inhibiting hormone (Part II, § 3); but it is probable that the time required for moulting would be more than the 23 days of the experiments summarized in Table 23 (Neiland and Scheer, 1953).

TABLE 23. CHANGES IN BODY COMPOSITION OF CRABS (*HEMIGRAPSUS NUDUS*) FOLLOWING STARVATION AND SINUS GLAND REMOVAL

All values are given on a wet weight basis and are means of measurements on two to four individuals (cf. Table 20). The changes in protein content, following the operation, are significant and are shown in italics (from Neiland and Scheer, 1953).

	NORMAL		STARVED 23 DAYS		STARVED WITH SINUS GLAND REMOVED	
Sex	M	F	M	F	M	F
Body weight, g	10·5	9·3	9·5	7·4	10·3	7·4
Glycogen, mg/g	0·69	1·24	0·8	0·8	0·76	1·02
Protein, mg N/g	12·71	14·96	12·08	12·08	*10·39*	*10·40*
Chitin, mg glucose equivalent/g	3·91	4·23	3·89	4·09	3·49	4·14

The results may be taken to represent the intermoult situation. The effects of fasting and the technique of sinus gland removal in *Hemigrapsus* have been referred to already in relation to reduction of fat (§ 5.112). Their effect upon glycogen "which might be regarded as the most logical source of glucose and of chitin", is not appreciable, and supports the suggestion that the crabs were not near moulting, when new chitin is formed. There appears to be a certain weight loss, which is reasonable in starved animals; but it would not occur in those from which removal of eyestalks was inducing moulting, as this is accompanied by increased water uptake (§ 5.321). It is claimed that in these conditions the reduction in total nitrogen is significant, and represents the effect of removing an eyestalk hormone that normally restrains protein catabolism.

This hormone may be the same as the moult-inhibiting hormone.

Increased loss of proteins following eyestalk removal is also claimed for *Carcinus* from measurement of nitrogen excretion. This is partly due to the stress of wounding, since a similar effect, but of only half the magnitude, results from leg amputation (Needham, 1955). As no hormone injections were used to counteract this effect, the evidence is not conclusive; but it again suggests that in non-moulting crabs an eyestalk hormone restrains protein breakdown.

During moulting the situation is different. Although the protein content of the plasma is unusually high because of resorption from the old skin, nitrogen excretion is particularly low. Needham (1957) concluded that "within limits the animal is able to control its nitrogen output, whatever the external conditions". As moulting proceeds most of the protein from the plasma is presumably deflected into certain anabolic processes, such as the formation of the new integument. These protein transfers would not of themselves alter the total proteins in the body. Nor does starvation affect the issue, since most crabs do not feed for some days before, during or after moulting.

Koch (1952) confirms the view that the nitrogen and protein content of the body remains remarkably constant during moulting, and is not affected by the absence of any eyestalk hormone. Incidentally, the moult-inhibiting hormone is not released from the eyestalk at this stage (Part II, § 3). Koch examined the nitrogen content of the mitten crab, *Eriocheir sinensis*, and found that the eyestalks have no effect upon the nitrogen metabolism, at least during the first experimentally induced moult. There is no difference in the ratio of nitrogen content to size, in the cast skins of crabs moulting normally and those induced to do so by eyestalk removal. The ratio of total nitrogen content to carapace width measured before moulting is the same, within limits, for moulting and non-moulting control crabs, and for operated crabs (between curves, Fig. 5-11). After an induced moult, the ratio of nitrogen in body and cast skin to carapace width, measured after moulting in the operated crabs, is significantly lower (◩, Fig. 5-11) than before, by an amount that seems to be proportional to the increase in water content that follows from the absence of the diuretic hormone of the eyestalk (§ 5.321); but this is not shown quantitatively. Excessive water uptake cannot afford an explanation for the contrary findings in *Hemigrapsus*, where there is no weight increase (Table 23). Whether the abnormally large volume increase observed during the first moult, following eyestalk removal in *Eriocheir*, might be followed later by a correlated increase in tissue synthesis remains to be investigated. Recent evidence on moulting hormones makes a tentative interpretation of these events possible,

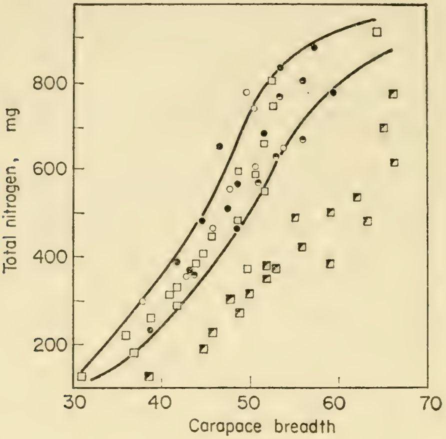

FIG. 5-11. Relation of the total nitrogen content of the crab, *Eriocheir sinensis*, to its size before and after moulting. The recorded values fall into three categories. (i) Total nitrogen in body (ordinates) measured before moulting and plotted against carapace breadth (abscissae): ● for non-moulting control crabs. (ii) Total nitrogen in body plus that in cast skin measured immediately after moulting and plotted against carapace breadth of *old* shell: ○ for control crabs moulting naturally; □ for eyestalkless crabs after forced moult. (iii) Same total nitrogen as in (ii) plotted against carapace breadth of *new* shell: ◓ for controls that still fall within normal range shown by curves; ◩ for eyestalkless crabs after forced moult due to loss of moult-inhibiting hormone, MIH. These show markedly low ratios and it is assumed that though loss of MIH does not affect nitrogen metabolism (ii), the loss of the DIURETIC HORMONE in the eyestalk allows increased water imbibition and swelling that increases the crab's size relative to its nitrogen content (from Koch, 1952).

if the apparent difference in nitrogen excretion in the intermoult and moulting periods may be taken as valid.

The intermoult period is characterized by secretion of the moult-inhibiting hormone, MIH, and the lack of any Y-organ secretion. Removal of the eyestalk, or even of the sinus gland, allows the Y-organ to come slowly into action. Normal moulting occurs when the secretion of MIH stops naturally and the moult-promoting hormone, MPH, from the Y-organ becomes active (§ 4.211 and Table 24).

From this it appears that during intermoult, the amount of protein catabolism, probably accompanied by steady synthesis, is restrained by MIH (as has been postulated) since lack of MIH results in increased catabolism. During moulting, catabolism and N-excretion are practically inhibited; since this cannot be attributed to the lack of MIH, it may perhaps be correlated with the presence of MPH from the Y-organ, which was absent during the intermoult period but is now active. The lack of excretion at this stage is accompanied by evidence of transfer of proteins to the new integument, and is a process so clearly related to moulting that it might well be under the control of the MOULT-PROMOTING HORMONE.

5.222 *Increase in protein synthesis*

INSECTA. Evidence from both *Periplaneta* (Bodenstein, 1953) and *Calliphora* shows that removal of either the MEDIAN NEUROSECRETORY CELLS OF THE BRAIN or of their stored products in the CORPORA CARDIACA results in reduced protein synthesis; in *Periplaneta* this is shown rather indirectly by the disappearance of urates from the fat bodies, and their re-formation after re-implantation of the corpora cardiaca. In *Calliphora* an effect upon protein synthesis is deduced from the reduction or cessation of growth of the ovaries, accessory glands, oenocytes and corpora allata after ablation of the neurosecretory cells (E. Thomsen, 1952 and 1956). The effect is similar to that of keeping the flies on a protein-free diet of sugar and water. The effect of removing the corpus cardiacum is similar to, but not so profound as, removing the source of the neurosecretion.

The removal of the CORPORA ALLATA of *Carausius* is followed by an increase in amino acids in the tissues, which is interpreted as

TABLE 24. HORMONES ASSOCIATED WITH NITROGEN EXCRETION IN CRABS

CRABS	STATE OF EYESTALKS	N-EXCRETION	HORMONES IN CIRCULATION	
			MIH	MPH
		INTERMOULT		
Hemigrapsus and *Carcinus*	intact	medium	present	absent (inhibited)
	removed	increased	absent (operatively)	absent (still not secreted during experiment)
		MOULT		
Eriocheir and *Carcinus*	intact	low	absent (no secretion)	present
	removed	low (no change)	absent (operatively)	present

MIH = moult-inhibiting hormone in eyestalk, apparently also restraining catabolism.
MPH = moult-promoting hormone from Y-organ in head, apparently associated with virtual inhibition of N-excretion and stimulation of protein transfer to new integument.

showing inhibition of protein synthesis (L'Hélias, 1953). This hormone, like that of the brain and corpora cardiaca, would therefore presumably favour protein synthesis.

It seems that secretion of these hormones in arthropods is stimulated mainly by the nervous system, with little trace of endocrinokinetic control (§ 4.21), unless the neurosecretion from the brain stimulates the secretion as well as the growth of the corpora allata; but on this the evidence is inconclusive (Thomsen, 1952). The neurosecretion does not pass into the blood.

5.223 *Decrease in protein synthesis or increase in protein catabolism*

CRUSTACEA. Evidence that in *Carcinus* the TIPS OF THE EYESTALKS stimulate catabolism, which is decreased by their removal, suggests the possible seat of a hormone that is antagonistic to those of the rest of the eyestalk (§ 5.221); but it is as yet unidentified (Needham, 1955).

VERTEBRATA. The hormone chiefly connected with increasing protein catabolism and possibly restraining synthesis in the vertebrates is one of those from the ADRENAL CORTEX (Chester Jones, 1957*a*); but results as yet seem to be rather contradictory, and it is not clear whether this is really due to specific differences, or to the restriction of different reactions to different organs in the body.

MAMMALIA. The state of nutrition of the animals is important: in starvation, the administration of adrenocortical hormones of the HYDROCORTISONE type causes a much greater increase in protein catabolism than it does in well-fed animals. Both stress and ACTH (§ 4.231) injection into nephrectomized rats cause an increase in urea formation, which is restrained by glucose injections. In part, this may be due to the concurrent action of the hormones concerned with carbohydrate metabolism (Noble, 1955).

It is clear that the endocrinokinetic control exercised by ACTH, from the adenohypophysis, plays an important part in these animals, in contrast to the situation in the Arthropoda.

5.3 Balance of monovalent electrolytes and water

The control of salts and water in the blood and tissues is of importance to all animals living in environments with which they are not in osmotic and ionic equilibrium; but evidence of this control being exerted by hormones is almost confined to the vertebrates. Hormonal control of these factors among invertebrates is as yet only known in relation to water in a few arthropods.

There are, from the point of view of basic physiology, two contrasting situations in which an animal must be able to control its salt and water content if it is to survive. In the first, the blood and tissues tend to lose salts and become diluted by imbibition of water. This can arise when an aquatic animal moves into any hypotonic medium; but it is particularly associated with the migration from the sea to fresh water. Since the salt losses cannot, as a rule, be made good merely from the food, most freshwater animals not only reabsorb salts from their urine but also absorb them from the environment against considerable osmotic gradients. This involves the active transport of ions across certain cell membranes (cf. Kitching, 1957). There are various hypotheses concerning active transport, but they may all "be expected to contain the following principles:

(a) The cations [such as Na^+] are not transported as the free ions, but are bound in some complex, which operates as a carrier;

(b) This carrier operates in a cyclical manner across a membrane. Towards one side of the membrane it combines with the ion and towards the other side it releases the ion, the process being combined either with an exchange for another cation or it is accompanied by an anion [such as Cl^-]. These associated exchanges may or may not be active in turn;

(c) The release of the ion must be associated with a simultaneous release or transfer of the necessary energy if osmotic work is being done" (Conway, 1956).

At the same time, water which enters the tissues by endosmosis from a hypotonic medium must be baled out by some form of increased diuresis, either by a contractile vacuole or some other form of excretory organ. Movement of both salts and water may be controlled by hormones.

In the second situation, the salts in the blood and tissues tend to become concentrated by water loss, with or without simultaneous salt endosmosis. This can occur when animals migrate to land where dehydration and thirst are the main dangers, even though water losses through the skin may be virtually abolished; for losses through the respiratory surfaces and by excretion are inevitable. The main response to these water losses is hormonally controlled antidiuresis, involving reabsorption of water from the urine. In addition to this, the Amphibia and some insects can absorb water through the skin. Dehydration and salt increase also occur when animals move into any hypertonic aquatic medium; for instance, when teleosts migrate back to the sea, after having acquired a lowered salt content during their sojourn in fresh water. Here the necessary dilution and proportion of the salts in the blood is maintained, chiefly by active excretion of sodium and chloride ions either through the gills or the kidneys; there may also be antidiuresis, but the action of hormones that control this in fish is less clear than in tetrapods.

Although in a stable environment little control may be required, most animals maintain a dynamic equilibrium between these two extremes; for the normal response to either hydration or dehydration (if carried to the limit) would lead to the opposite state being reached in the tissues. Control that allows of a variable response is demanded in particular of those animals which migrate periodically, like some estuarine crustaceans and fish, between fresh waters and the sea. They must be able to contend alternately with flooding of their tissues with water in one environment, and their dehydration by the high salt concentration of the other. In most of these cases, however, all too little is yet known of the part played by hormones.

In those mammals, where the position is best understood, four hormones are probably concerned: one antagonistic pair to control the movement of salts and another pair for the water balance. Complete elucidation is still difficult, not only because the movements of salts and water are so intimately linked by osmotic forces, but also because the associated hormones, active in a given

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TABLE 25. METABOLIC HORMONES CONTROLLING ELECTROLYTES AND WATER

	EFFECT	VERTEBRATE		INVERTEBRATE	
		ORGAN OR HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
5.31	SALT BALANCE				
5.311	*Increase in* Na$^+$ *and* Cl$^-$ *in blood* (active reabsorption)	Adrenal cortex (aldosterone)	*Rana* Reptiles Mammals	—	—
	K$^+$ *excretion*	,,	Mammals	—	—
5.312	*Decrease of* Na$^+$ *and* Cl$^-$ *in blood* (excretion)	Neurohypophysis (oxytocin)	Axolotl Mammals	—	—
	K$^+$ *retention*	,, ?	Mammals	—	—
5.32	WATER BALANCE				
5.321	*Decrease in permeability and diuresis*	Corpuscles of Stannius ?	Teleosts	Ganglionic-X-organ/sinus gland	*Cambarus* *Astacus* *Carcinus*
		Adrenal cortex (hydrocortisone)	*Rana* (kidney) Reptiles Mammals	Brain and/or C. cardiaca	*Anisotarsus* *Blaptica* ?
		Thyroid (thyroxine)	Teleosts Mammals		
5.322	*Increase in permeability and antidiuresis*	Neurohypophysis (antidiuretic) ADH	Teleosts ? *Rana* *Bufo* $\left\{\begin{array}{l}\text{skin}\\ \text{kidney}\\ \text{bladder}\end{array}\right.$ Reptiles Birds Mammals	Post salivary gland ?	*Octopus*

situation, are derived from the same source and are closely related chemically (Fig. 5-15).

There are indications of a similar type of hormone control occurring in other vertebrates; but the evidence is less conclusive, and workers are not in full agreement. There is, as yet, practically no evidence to show whether the same form of control occurs in any invertebrates.

The hormonal control of salts will be considered first (§ 5.31), and that of water afterwards (§ 5.32), since the direction of movement of the water is so often determined by that of the salts.

5.31 BALANCE OF SODIUM IONS (Na^+) AND OF ASSOCIATED MONOVALENT ELECTROLYTES (K^+ AND Cl^-)

5.311 *Increase of* Na^+ *in the blood*

Active transport of ions across living membranes and especially the so-called "sodium pump" are now well-known phenomena in invertebrates as well as vertebrates.

Invertebrates. Both crustaceans and insects living in fresh water are known to take up sodium and chloride ions from the surrounding water by active transport, through the gills in *Eriocheir*, and by the anal papillae in the larval *Chironomus*; but, as yet, there is no evidence of any hormonal control of these activities. Although the isolated gills of *Eriocheir* make a beautiful preparation for demonstrating active transport of sodium, they have not apparently been examined for the effects of possible hormones; drugs have, however, been shown to have closely comparable actions here and on frog skin (Koch, 1954).

Vertebrata. A number of cases now indicate some hormonal control of active transport of ions across cell membranes in vertebrates. This transport involves the use of metabolic energy, derived from aerobic respiration, to overcome the osmotic gradient. The action is stopped by lack of oxygen. Since among cold-blooded vertebrates much more is known of the situation in Amphibia than in Teleostei, they will be considered in that order.

Concentration of the blood by inward passage of salts through the skin

Amphibia. The skin of the frog plays an important part in maintaining the internal salt concentration well above that of the freshwater medium, and its action is facilitated by hormones of the ADRENAL CORTEX.

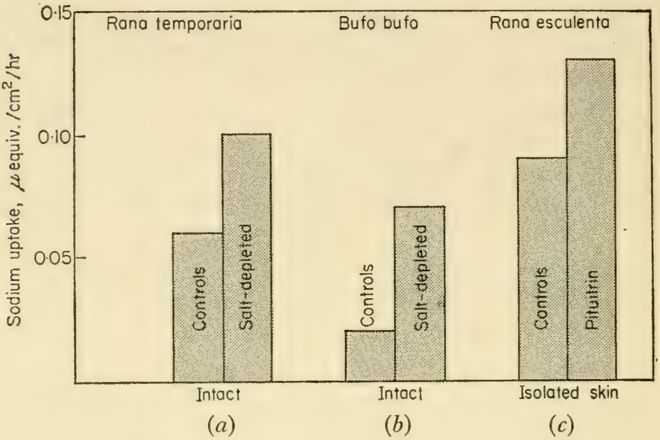


FIG. 5-12. Increase in the apparent rates of active sodium-ion uptake through the skin, produced by salt-depletion of (*a*) the intact common frog and (*b*) the toad (after Jørgensen). (*c*) The apparently similar effect of Pituitrin (a neurohypophysial extract) on the isolated skin of the edible frog (from Fuhrman and Ussing, in Sawyer, 1956).

In the intact animal there is evidence for independent absorption of both sodium and chloride ions against the osmotic gradient (Jørgensen, Levi and Zerahn, 1954), from external concentrations as low as 10^{-5} M.NaCl. Like the gills of *Eriocheir*, even the isolated frog's skin passes ions through itself from the outer surface to the inner ("controls", Fig. 5-12 *a–c*) by active transport. This transport is increased in intact frogs and toads after the tissues have been depleted of salt by "washing" in distilled water for some time (Fig. 5-12*a* and *b*). Since salt uptake is reduced in adrenalectomized animals, it is assumed that hormones of the adrenal cortex may stimulate the active transport of sodium ions inwards through the skin, as they do through the kidney tubules (see below).

Despite the fact that the action of extracts of the adrenal cortex in causing a marked increase in Cl⁻ uptake is similar to their action on Na⁺, it cannot be assumed that the transport of chloride ions follows passively upon that of sodium, since the rate of uptake of the two ions through the skin has been shown to be independent.

In the intact animal the secretion of the adrenal cortex may be stimulated by adrenocorticotrophin ACTH, (§ 4.231), from the adenohypophysis.

The effect of Pituitrin, an extract in this case of the neurohypophysis of a whale, on the sodium uptake of isolated skin (Fig. 5-12*c*) seems anomalous. The Pituitrin used was believed to be free of anterior lobe contamination, and therefore of ACTH, but oxytocin and antidiuretic hormone, ADH*, were certainly present in the extract and the latter caused so great a concurrent uptake of water that, although the absolute amount of sodium was increased as shown, the net effect was actually dilution (Sawyer, 1956). It would be curious, in view of the situation in other vertebrates, if neurohypophysial hormones should aid the uptake of salts in amphibians.

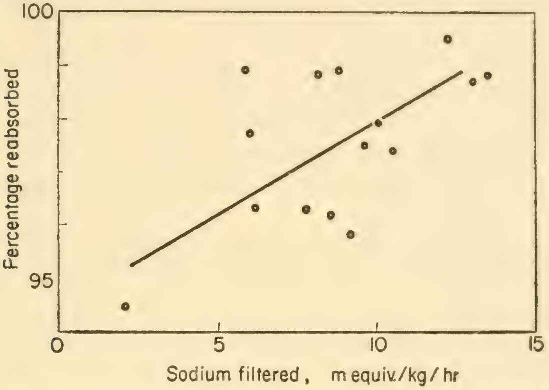


FIG. 5-13. Relationship between the percentage of the sodium reabsorbed from the kidney tubules (ordinates) and the total amount of sodium filtered through the glomeruli of the kidneys in m.equiv/kg/hr (abscissae) in the bullfrog, *Rana catesbiana*. The percentage is high over a wide range of concentrations of sodium in the tubules (from Sawyer, 1956).

* = vasopressin.

Concentration of the blood by reabsorption of salts through the kidney

AMPHIBIA. In most circumstances, and especially in fresh water, the function of the kidney is to reabsorb sodium (Na^+), and possibly chloride ions (Cl^-) actively, and to excrete a certain amount of potassium (K^+). Figure 5-13 shows that, over a wide range of sodium ion concentrations in the glomerular filtrate, at least 95 per cent is reabsorbed in the tubules. Active transport of sodium here is comparable with that through the skin. In adrenalectomized frogs sodium is excreted more rapidly (presumably because less is reabsorbed) than in normal controls (Fig. 5-14). There is a slight concurrent increase in muscle potassium (Fowler, 1956). Moreover, saline treatment can maintain life in the adrenalectomized frog, as it can in mammals. This seems to support the case for supposing that an adrenocortical hormone (ACH) is concerned in stimulating salt reabsorption in the kidney tubules of frogs, as in mammals.

It may well be that ACH secretion in Amphibia is under the endocrinokinetic control of ACTH (§ 4.231), since hypophysectomy is followed by symptoms closely similar to those resulting from adrenalectomy; other evidence is, however, defective (Chester Jones, 1957*a*).

TELEOSTEI. The established function of the adenohypophysis in protecting some teleosts, such as *Fundulus* (Burden, 1956), against the osmotic stress of transfer from sea water to fresh is probably endocrinokinetic; it seems to favour the retention of sodium and, more particularly, of chloride ions; but it is not yet clear if this is due to the release of adrenocorticotrophin, ACTH (§ 4.231), or of thyrotrophin, TSH (§ 4.221). Neither of these are replaceable by the corresponding mammalian hormone, and it has even been postulated that some other "unknown factor" may be present in the hypophysis of euryhaline teleosts. ACTH might be expected to stimulate secretion by the ANTERIOR INTERRENAL BODIES, which are the homologues in fish of the tetrapod adrenal cortex; but they do not seem to have been investigated in this connection (Rasquin and Rosenbloom, 1954). The effect of injecting extracts of adrenal cortex into trout has only been examined in the converse situation of their being exposed to excess salinity in sea water (see below).

The suggestion that the hypophysis acts by secretion of TSH arises from the fact that the THYROID, which it would stimulate, is active during the upstream (anadromous) migration of salmon and

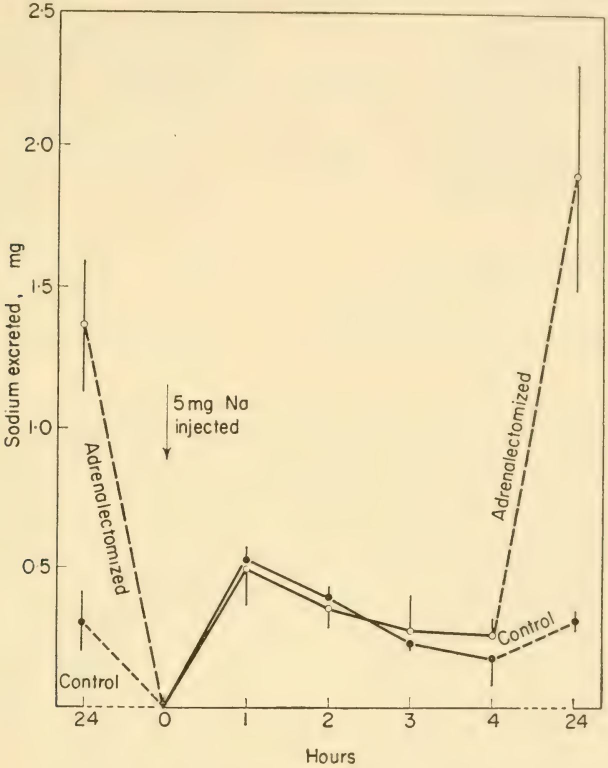
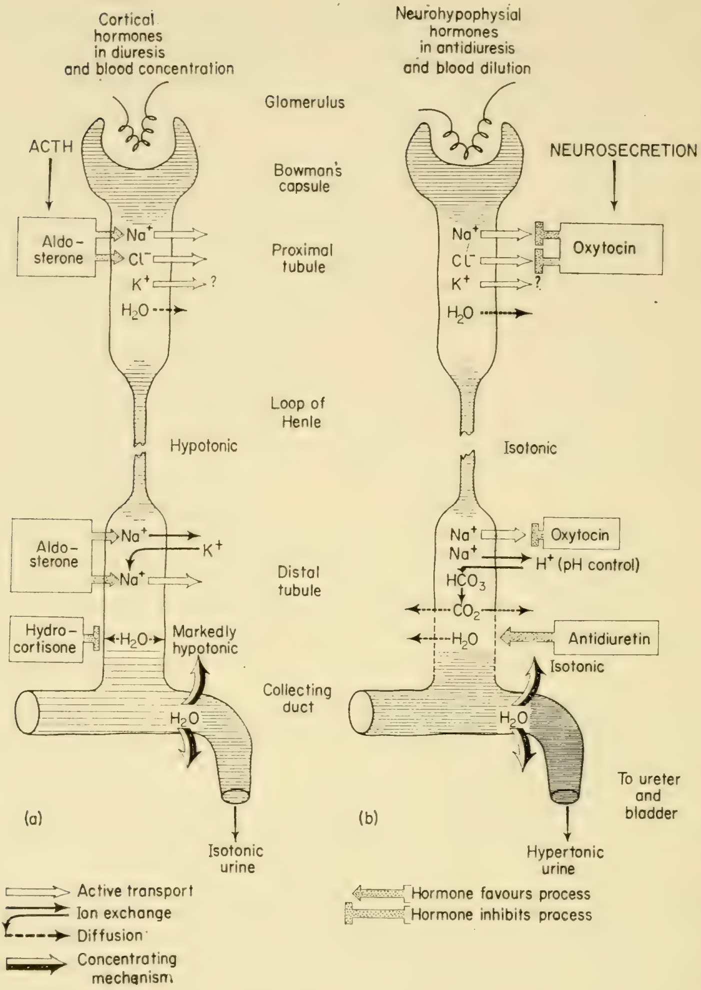


FIG. 5-14. Loss of sodium by excretion (ordinates) in hours (abscissae) from nine adrenalectomized frogs, *Rana*, (above) and from nine controls (below). After 24 hr in distilled water, (at hour 0) 5 mg Na (as frog Ringer solution) was injected into the dorsal lymph-sac of each, and excretion was recorded for the first 4 hr and at the end of 24 hr (points shown with standard deviation). Note the much greater excretion of sodium from the adrenalectomized frogs (from Fowler in Chester Jones, 1957).

eels from the sea. Since these fish show a concurrent phase of growth and maturation, it seems more probable that the thyroid



Cortical hormones in diuresis and blood concentration
Neurohypophysial hormones in antidiuresis and blood dilution
Glomerulus
ACTH
Bowman's capsule
NEUROSECRETION
Aldo-sterone
Na^+
Cl^-
K^+
?
H_2O
Proximal tubule
Oxytocin
Loop of Henle
Hypotonic
Isotonic
Aldo-sterone
K^+
Distal tubule
Oxytocin
H^+ (pH control)
HCO_3
CO_2
Hydro-cortisone
Markedly hypotonic
Antidiuretin
Isotonic
Collecting duct
H_2O
To ureter and bladder
(a)
(b)
Isotonic urine
Hypertonic urine
Active transport
Ion exchange
Diffusion
Concentrating mechanism
Hormone favours process
Hormone inhibits process

FIG. 5-15. Diagrams to show the action of hormones on the kidney tubules of a mammal. *a*. The cortical hormones, active in blood concentration: ALDOSTERONE, increasing reabsorption of salts, and HYDROCORTISONE, increasing water diuresis; obligatory endosmosis is then limited by the diffusion rate to about 80% of completion. In the loop of Henle the urine still has "free" water. *b*. The neurohypophysial hormones, active in blood dilution:

may be concerned with these processes than with osmotic regulation. Yet osmotic regulation also requires an increase in metabolic energy that might be stimulated by thyroxine (§ 5.111); it is noteworthy that the thyroid is more active in conditions of changing salinity than in stable conditions, even if these are abnormal (D. C. W. Smith, 1956). Experimental investigation of fish is clearly fraught with many difficulties; recently Jorgensen and Rosenkilde (1956) have issued a timely warning, in the form of observations on the very wide range of spontaneous variations that occur in the chloride content of relatively undisturbed and undamaged starving goldfish.

REPTILIA. Little is known of the electrolyte control in this class of vertebrates, but it is attractive to speculate that secretions of the ADRENAL CORTEX may act at the renal tubular level in reptiles to increase potassium excretion and sodium retention (Chester Jones, 1957*a*).

MAMMALIA. Hormones from the ADRENAL CORTEX (Fig. 5-15*a*). facilitate active transport of ions from the lumen of each convoluted kidney tubule into its cells, the surfaces of which are increased by a brush border. Reabsorption of sodium (Na^+) and potassium ions (K^+) from the glomerular filtrate, which is isosmotic with the plasma, occurs in the proximal tubules. Chloride ions (Cl^-) also move back into the cells in the same region, either by independent active transport, or in company with the cations, because of the difference in electric potential set up by the cation transport across the cell surface.

Cortical insufficiency, or removal of the adrenal cortex, is followed by loss of Na^+ from the plasma and tissues and its excretion in the urine (Fig. 5-16 and Table 26). The sodium

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OXYTOCIN, increasing salt excretion so that endosmosis can keep pace with the reduced rate of salt reabsorption; and ANTIDIURETIC HORMONE (vasopressin or ADH), increasing water reabsorption and reducing urine output (antidiuresis). The reactions in the tubules are similar to those in the Amphibia; but the mammal is peculiar in having a urine concentrating mechanism, probably in the collecting ducts (large arrows). More concentrated urine is indicated by closer striations.

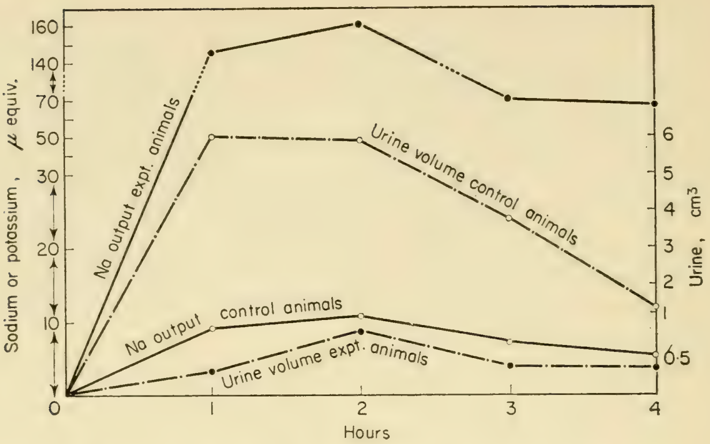

FIG. 5-16. Volume of urine and the micro-equivalents of sodium ions excreted by normal (control) and adrenalectomized (expt) male rats, *Rattus*, over a 4 hr period after administration of water by stomach pump (roughly 11 ml was given to each rat, according to its size, 1 hr before the record started and again at hour 0 to inhibit ADH secretion). Food was removed 24 hr beforehand. Note the poor water excretion by the adrenalectomized animals (lack of DIURETIC HORMONE) but their very high output of sodium (lack of ALDOSTERONE, cf. Fig. 5-15). The simultaneous output of potassium, though not shown, was little altered (from Chester Jones, 1957).

balance can be restored by injection of ACH, particularly ALDOSTERONE, though corticosterone is also effective (Chester Jones, 1957*a*). Although hydrocortisone can be present in 30 times the concentration of aldosterone in the blood, the latter is 300 times as potent in controlling the Na^+ balance and possibly that of Cl^-. It also has an action on the Na^+/K^+ ratio of salts excreted by the sweat and salivary glands (Simpson and Tait, 1955).

Table 26 shows that the effect of adrenalectomy on the plasma potassium, K^+, in rats is opposite to that on sodium. This is in part due to the effect of ion exchange in the distal tubule (Fig. 5-15*a*). Sodium loss and potassium retention seem to be major factors in causing the death of adrenalectomized animals, though the former is the more important, since life can be maintained, despite high blood potassium, as long as a high level of sodium chloride is given in the diet.

TABLE 26. CHANGES IN SODIUM AND POTASSIUM CONCENTRATION OF PLASMA AND MUSCLE, FOLLOWING ADRENALECTOMY

The changes are shown for groups of female rats, with and without diabetes insipidus (induced by removal of their neurohypophysis, which is the source of ADH). The figures are means, ± standard error (from Chester Jones, 1957 *b*).

GROUP	NUMBER OF SPECIMENS	BODY-WEIGHT g	PLASMA MEQ/l.*		MUSCLE		
					MEQ/KG. WET WT.		% WATER
			NA	K	NA	K	
Controls	12	190·63 ±4·94	148·36 ±4·22	4·96 ±0·22	23·39 ±0·31	100·26 ±0·99	75·43 ±0·33
Diabetes insipidus for 2 to 3 months	9	176·85 ±2·61	146·40 ±1·81	4·93 ±0·19	25·95 ±1·48	99·26 ±1·63	75·78 ±0·29
Controls adrenalectomized for 8 days	12	189·88 ±5·90	131·85 ±2·70	7·84 ±0·13	18·33 ±1·49	110·08 ±1·92	76·60 ±0·39
Diabetes insipidus, adrenalectomized for 8 days	10	196·50 ±5·50	146·16 ±3·10	6·03 ±0·18	19·68 ±0·60	105·18 ±1·82	76·00 ±0·67

* milli-equivalents per litre.

Aldosterone is secreted in response to adrenocorticotrophin, ACTH, in rats, but not in the human (§ 4.231).

5.312 *Decrease of* Na^+ *in the blood*

There is no evidence for any hormones stimulating Na^+ and Cl^- excretion in invertebrates, and so far it is rather tentative in vertebrates, especially in the cold-blooded classes.

AMPHIBIA. It has been shown that injection of a neurohypophysial extract containing OXYTOCIN increases Cl^- excretion in the axolotl (Sawyer, 1956).

TELEOSTEI. Most marine teleosts maintain their body fluids at a lower level of salt concentration than that of the sea, by means of specialized salt excreting cells on the gills. If any of the endocrine organs are concerned in stimulating this process, their action has not yet been proved. Extracts of mammalian adrenal cortex, ACH, have been injected into trout in sea water, and have been found not to increase their survival time in the excessively saline medium. Despite the fact that in other vertebrates ACH causes an increase in salt reabsorption rather than its excretion, the author suggests trying even larger doses (D. C. W. Smith, 1956). A single test of mammalian neurohypophysial extract likewise failed to increase the survival time of these trout, although it increases salt excretion in mammals. It is known that other teleostean hormones are very specific; also that the neurosecretory store in the neurohypophysis of *Callionymus* is depleted when this teleost is exposed to a hypertonic medium (Arvy, 1957). It might, therefore, be expected that extracts of fish neurohypophysis might be more successful than mammalian hormones in increasing salt excretion. On the other hand, salt excretion by the gills may be under quite other control than that by the kidneys.

AVES. The nasal glands of the cormorant, *Phalacrocorax*, and probably of other oceanic birds* secrete salts, enabling them to eliminate excess Na^+ and Cl^- taken up from any hypertonic media in which the birds may feed (Schmidt-Nielsen *et al.*, 1958). It is not yet known if this active transport is under hormonal control, as might be expected.

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* The need for some such mechanism for flamingoes feeding in highly alkaline water had already been indicated (Jenkin, 1957).

MAMMALIA. Removal of the neurohypophysis, and therefore of the supply of OXYTOCIN from rats (last line of Table 26), mitigates considerably the effects of adrenalectomy, at least as far as plasma sodium is concerned. Plasma sodium is practically equivalent to that of the control, and potassium is lowered, as compared with specimens that had had the adrenals only removed; plasma potassium is, however, not fully restored to normal, and the balance of ions in the muscles is decidedly abnormal. A series of such experiments shows that the neurohypophysis is at least partially responsible for the loss of sodium in adrenalectomized animals, and that its action must be to inhibit the active tubular reabsorption of sodium ions (Fig. 5-15*b*). Its action on chloride ions may be similar to that on sodium; but that on potassium is, as yet, far less clear (Chester Jones, 1957*a*).

The interesting if tentative suggestion has been made that the effect of neurohypophysial removal may be due to the loss of the oxytocin secretion, rather than the antidiuretic fraction, ADH. Injections of oxytocin, at least in pharmacological doses, are more effective than ADH in increasing sodium excretion in dogs with a low rate of urine flow (Brooks and M. Pickford, 1957).

If this last suggestion is further substantiated, the situation would be that sodium as well as chloride ions, at least in rats (Dicker and Heller, 1946), are controlled by the balance between aldosterone, favouring their reabsorption, and oxytocin, favouring their excretion. Potassium ions are excreted during periods of aldosterone activity. Secretion by the adrenal cortex is usually stimulated by ACTH, but this has less effect upon aldosterone than on other cortical hormones; the only control of neurohypophysial secretion is nervous.

5.32 WATER BALANCE

The direction of movement of water through a cell surface is determined by osmotic forces; but the rate of movement can be affected by hormones, which vary the permeability of the surface. Decrease in permeability, which is associated with diuresis, will be considered first (§ 5.321), as it tends to concentrate the blood salts and to accompany salt reabsorption (§ 5.311); increase in permeability associated with antidiuresis will be taken second

(§ 5.322), since, like salt excretion (§ 5.312), it tends to dilute the blood-salts (Table 25). Such hormones are well-established in Arthropoda as well as in Vertebrata. In the latter, the hormones tending to concentrate the blood come from the adrenal cortex, and those tending to dilute it from the neurohypophysis, as they do for the control of Na^+ and Cl^- (Fig. 5-15).

5.321 *Decrease in cell permeability and diuresis leading to concentration of the blood*

Crustacea. Water uptake is a normal accompaniment of moulting, and probably plays a crucial part in helping to force off the old cuticle. In the crayfish, *Cambarus*, eyestalk removal induces both precocious moulting and abnormally great water uptake (from 23 to 50 per cent of the body weight) during premoult; but this can be reduced again to about the normal level by implantation of two sinus glands (Scudamore, 1947; Fig. 5-17). Opinions differ as to whether eyestalk removal has a significant effect upon the water

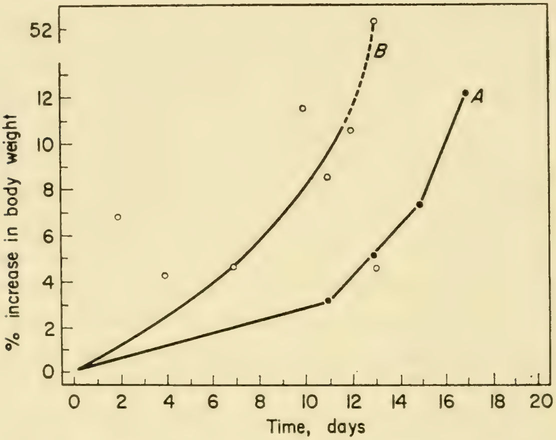

Fig. 5-17. Percentage increase in water content (ordinates), as measured by changes in body weight in the crayfish, *Cambarus immunis* and *C. propinquas*, during 16 days (abscissae) after eyestalk removal. Black circles show values for one specimen with two sinus gland implants (curve A). This specimen shows less water uptake than the mean for eight eyestalkless controls with no implants (open circles, curve B). (From Scudamore, 1947).

uptake of the fiddler crab, *Uca* (Scudamore, 1947 and Guyselman, 1953); but in the shore crab, *Carcinus*, as in *Cambarus*, eyestalk removal before moulting results in a volume increase of 180 per cent instead of 80 per cent in the normal crab. Injected sinus gland extracts reduce the former value to 80 per cent and the latter to 50 or 60 per cent (Carlisle, 1956).

At premoult, when the natural secretion of moult-inhibiting hormone begins to fade out, there is known to be an increase in internal osmotic pressure, owing to the mobilization in the blood of materials resorbed from the old skin. In forced moults, following eyestalk ablation, water absorption is greater than in natural moults, although this mobilization proceeds more slowly. The change in internal osmotic pressure in forced moulting cannot therefore be the only cause of increased water uptake. The loss of eyestalks and their hormones must increase the permeability of the tissues to water, as well as inducing the moult and the increase in osmotic pressure. Swelling at the time of natural moulting must then be due to a decrease in the secretion of this hormone, but not to its complete cessation. This would allow the skin, and particularly the branchial epithelium, to become more permeable than in the intermoult stage, but not as permeable as in forced moults. Increased permeability of the excretory tissue would also allow of increase in reabsorption of water from the urine, but there seem to be no figures relating to urine flow during moulting.

Even under natural conditions in sea water, there must be considerable water endosmosis in *Carcinus* to maintain the high rate of urine flow, amounting to 14 per cent of the blood volume daily. The necessary internal osmotic pressure to achieve this, (unless active transport of water is to be postulated) must be partly due to active inward transport of such ions as Na^+, Ca^{++} and Cl^-; but this is small, though it may, perhaps, be aided by the presence in the haemolymph of ionized proteins, which do not pass into the urine. At the same time the endosmosis must be limited by a certain degree of impermeability of the tissues, maintained by the eyestalk hormone, otherwise eyestalk removal would not result in increased water uptake. It therefore seems reasonable to postulate that the action of one of the eyestalk hormones is the same as that of other diuretic hormones, namely, to decrease the permeability of the skin and of the excretory organs.

In a dilute medium such as 50 per cent sea water, active transport of ions is increased, gill permeability is decreased, and urine flow is increased to about 24 per cent of the blood volume daily. At the same time there is a limited swelling of the tissues (Webb, 1940). The increased diuresis is presumably achieved by an increased secretion of the diuretic hormone from the sinus gland causing increased impermeability of the kidney tissues, as well as of the gills.

Carlisle (1956) has claimed that the DIURETIC HORMONE of *Carcinus* differs from the moult-inhibiting hormone that is also obtained from the eyestalk, because only in the winter, at least at Plymouth, could he extract a moult-inhibiting substance, even from the sinus glands of the same species; extracts of SINUS GLAND from a number of other Crustacea were effective at all times of the year in reducing water content. The diuretic extracts could not be obtained from the cerebral ganglia, although these yield a strong moult-inhibiting extract. Passano (1953) claims that the differences are quantitative and that the tissues have a lower threshold value of sensitivity to the water-balance effect than to the moult-inhibiting hormone.

The observation that eyestalk removal reduced deaths of *Carcinus* from exposure for 24 hr to conditions of lowered salinity (Knowles and Carlisle, 1956) remains obscure. Survival would seem to require the presence, rather than the absence, of the diuretic hormone in the eyestalks. (Carlisle, *in lit.* 4.3.1957, agrees that the situation is far from clear, and thinks that perhaps in Crustacea, as in vertebrates, the balance of water, or of water and salts, is under the control of two hormones. The moult-promoting hormone from the Y-organ may be one of them.)

INSECTA. A DIURETIC HORMONE has been claimed for the beetle larva, *Anisotarsus cupripennis*, and perhaps for other insects such as *Blaptica* (Nuñez, 1956). It appears to be secreted by the BRAIN, and is possibly stored in the CORPORA CARDIACA, which were not separated from the brain in the experiments. The larva lives in a damp environment and can take up water by endosmosis through the integumental cells lining the tracheoles; but it normally remains constant in size and weight by excreting the excess water into the

Malpighian tubules (Fig. 5-18, upper specimen, and Fig. 5-19*a*, dotted curve). If either the neck is ligatured or the head is cut off, preventing any flow of hormone to the body, or if the source of hormone is removed by ablating the upper part of the brain, the operated specimen swells steadily by retention of water (Fig. 5-18, lower specimen, and Fig. 5-19*a*, full curve). Injection of brain extract restores the water balance, presumably by increasing excretion (Fig. 5-19*b*, full curve); but extracts of suboesophageal ganglion have no such diuretic effect (Fig. 5-19*b*, dotted curve).

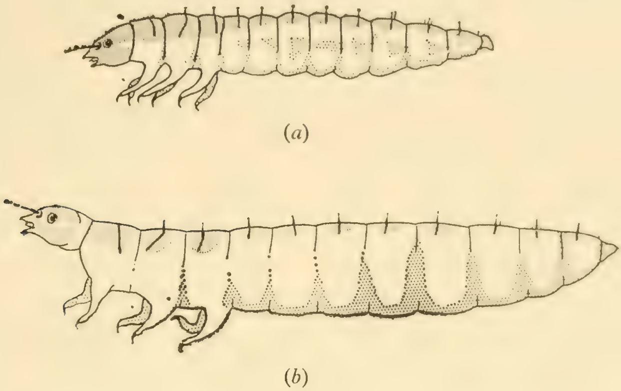

FIG. 5-18. Water uptake in larvae of the beetle, *Anisotarsus cupripennis*. *a*. Normal larva, and *b*. operated larva to show the swelling due to water uptake after removal of the upper part of the brain, including the CEREBRAL NEUROSECRETORY CELLS, and the corpora cardiaca (from Nuñez, 1956).

The seat of action of this DIURETIC HORMONE does not seem to have been established, but it acts on excretion rather than on water uptake. Probably it inhibits the reabsorption of water as it passes from the Malpighian tubules through the intestine. If so, a decrease in cell permeability in the intestine could be responsible, and would be comparable with that occurring in the skin of *Carcinus*, or in the distal kidney tubules of vertebrates, during diuresis.

One curious feature is that the secretion of this metabolic

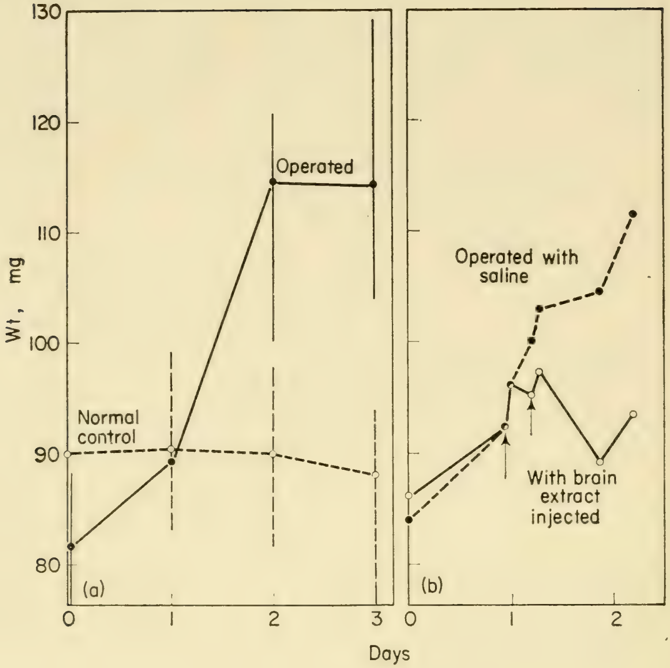

FIG. 5-19. Water uptake in larvae of *Anisotarsus*. *a*. The dotted line gives the mean weight (ordinates) in 3 days (abscissae) for five normal larvae, which remain constant in weight by diuresis. The full line gives the mean weight of five initially rather smaller, operated larvae (as Fig. 5-18*b*) over the same period. Vertical lines show the range of weights between the extremes in each group. These do not overlap after the first day. *b*. Effect of injected extracts made at the times marked by arrows. The curves give weights of individual larvae, in which secretion of their own hormone was prevented by section of the circumoesophageal connectives. The full line shows an arrest in water uptake, *i.e.* facilitation of diuresis, following injection of an extract of brain and corpora cardiaca in 1% NaCl. The dotted line shows continued water uptake after injection of a control extract of suboesophageal ganglia in 1% NaCl; salt solution alone gave a similar result (from Nuñez, 1956).

hormone is stimulated nervously from the ganglionic network round the gut; if this is damaged, or if the circumoesophageal connectives to the brain are cut, hormone secretion is not induced when the abdomen begins to swell. This nervous stimulation of hormone secretion recalls the activation of the pigment-controlling hormone of *Carausius* (§ 3.221), but is unusual for a metabolic hormone (§ 5.522), unless it be for the neurohypophysial hormones (§ 5.322).

VERTEBRATA. HYDROCORTISONE*, from the ADRENAL CORTEX (§ 2.31), has been found to have a diuretic effect on the kidneys, and also on the skin, of some vertebrates; but the evidence is most definite for amphibians and mammals (Table 25).

AMPHIBIA. When amphibians enter their normal freshwater environment, excess water tends to enter through any permeable tissues and to dilute the salt concentration in the blood.

No observations on the action of hormones on the skin have so far been recorded in connection with limiting this endosmosis; it would clearly be of interest to know whether the relative impermeability that is usual for the skin (controls, Fig. 5-20 *a-c*,) results merely from the lack of antidiuretic hormone, (§ 5.322), or whether a positive, pore-contracting action of an adrenocortical hormone may also be involved. The similarity in behaviour between isolated skin and that in whole animals would lend no support to the latter supposition, unless hydrocortisone persists for a long time in the tissues after isolation.

The reactions are slightly better known in the kidney, where diuresis seems to be facilitated by HYDROCORTISONE. On exposure to a hypotonic medium, salts are actively reabsorbed in the proximal tubules (§ 5.311). This would result, as in the mammalian kidney (Fig. 5-15*a*, p. 214) in an obligatory endosmosis of water. In so far as the inward diffusion of water failed to keep pace with the transport of the salts, "free water" would remain in the tubules, converting the isosmotic glomerular filtrate into hypotonic urine. The greater the degree of impermeability to water possessed by the kidney tubules, the greater would be the hypotonicity of the urine. There is no clear evidence as to how this impermeability is maintained in frogs, but it is probable that hydrocortisone may act here as in mammals. The removal of such hormones by adrenalectomy in *Rana temporaria* (but not in *R. pipiens*) is followed by oedema, or an excessive accumulation of water in the tissues; but the effect of injecting cortical extracts has not yet been shown (Chester Jones, 1957*a*).

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* Several related 17–OH steroids have the same effect (Part II).

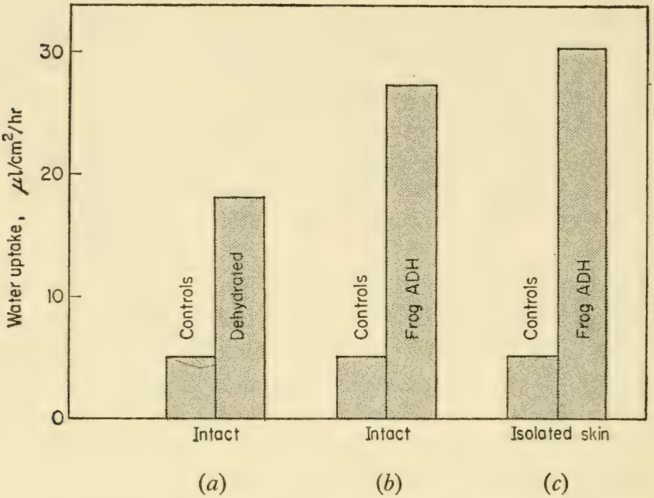

FIG. 5-20. Increase in rate of water uptake following dehydration or injection of neurohypophysial extract (frog ADH); *a.* and *b.* in intact *Rana pipiens*, with the cloaca ligatured to prevent loss by excretion; *c.* in isolated frog's skin (from Sawyer, 1956).

TELEOSTEI. Although freshwater teleost fish are in much the same osmotic relation to the environment as Amphibia, the scales usually make the skin more waterproof, and water only enters the tissues through the gut and gills. Diuresis by the kidneys seems therefore to be the main means of water control, and there is some evidence that the cortical cells of the ANTERIOR INTERRENAL BODY (§ 2.311) may be concerned; but the situation is different in species adapted to different normal environments. In *Fundulus*, the cortical cells remain inactive when the fish are in sea water, which is for them a hypertonic medium (cf. G. Pickford and Atz, 1957).

The protective action claimed for the thyroid, in allowing fish to migrate into waters of low salinity, has not been fully elucidated (cf. § 5.311); but it may be similar to that of thyroxine, in causing water (and salts) to pass from the tissues of mammals to their blood, thereby increasing the possible rate of water diuresis by the kidneys (Fontaine, 1956).

The corpuscles of Stannius, derived from the pronephric ducts of teleosts, may also have a diuretic function, as they tend to hypertrophy when the tissues are loaded with water (Rasquin, 1956).

MAMMALIA. When water is plentiful in the tissues, the mammalian kidney reacts like that of the frog and excretes a hypotonic urine. The volume of urine is considerably less than that of the glomerular filtrate, chiefly because reabsorption of salts by active transport in the proximal tubules results in a correlated reabsorption of at least 4/5ths of the water by obligatory endosmosis, either in the same part or in the thin loop of Henle. Nevertheless, the diffusion rate for water limits the amount of endosmosis, so that, as in the frog, "free water" remains in the tubule. Most of the remaining sodium ions are actively reabsorbed, or exchanged for other cations, and especially for H^+, in the distal tubule, which is made relatively impermeable by HYDROCORTISONE. This causes further water to become "free" and to pass on to the collecting ducts. Thence it would be excreted, as it is in the frog, were it not for a "concentrating mechanism", which is apparently independent of hormone control. This is of most significance in reinforcing antidiuresis, and it is referred to in more detail in that connexion (§ 5.322). "Osmotic diuresis" is also unaffected by hormones; it can occur if the blood is loaded with extra urea, which then passes into the glomerular filtrate and increases the tubular osmotic pressure. so that more water than usual is excreted, instead of being reabsorbed (Mudge, 1954).

The action of hydrocortisone, in causing the relative impermeability of the distal tubules in normal diuresis, has been examined indirectly in "water-loaded rats", i.e. rats which have been given large doses of water by stomach tube. Such rats normally show a maximal urine flow, comparable to that of rats with "diabetes insipidus", which follows inactivation, or removal, of the neurohypophysis and therefore of the store of the antidiuretic hormone (§ 5.322). When adrenalectomized, the water-loaded rats, with or without their neurohypophyses, show less than 1/10th of the urine flow of either unoperated or merely neurohypophysectomized controls (Chester Jones, 1957*b*; cf. Table 27).

The decrease in diuresis in adrenalectomized rats (Fig. 5-16, p. 216) is greater than could be accounted for by the decrease of the blood pressure to a half, or even the correlated drop to 1/6th in G.F.R., the glomerular filtration rate. It may be assumed to be due to the lack of adrenocortical hormones.

If rats are loaded with hypertonic saline, instead of water, the urine flow in the controls is halved, as compared with that in the rats with diabetes insipidus. This is mainly because the antidiuretic hormone, ADH, is secreted in response to increased tissue salinity and higher osmotic pressure of the blood (§ 5.322). Adrenalectomy, by removing the source of the diuretic hormone, reduces urine flow still further, though not so greatly as in the case of water-loading. This is because the higher level of salts in the glomerular filtrate reduces the volume of obligatory endosmosis. The action appears to be independent of the presence or absence of the neurohypophysis (see Chester Jones, 1957*a*, for further details).

The secretion of hydrocortisone, that causes relative tubule impermeability, is stimulated by adrenocorticotrophin, ACTH (§ 4.231).

5.322 *Increase in cell permeability and antidiuresis leading to dilution of the blood-salts*

Dehydration can occur both on land and in any hypertonic aquatic environment. The animals' response to this usually includes waterproofing some parts of the body surface to restrict water loss and increasing the permeability of other parts to allow of water uptake or reabsorption.

Invertebrates. No example of a hormone that increases tissue permeability to water has so far been found in the reports on

TABLE 27. CHANGES IN EXCRETION OF WATER, SODIUM AND POTASSIUM, FOLLOWING ADRENALECTOMY

The output of urine, sodium and potassium, the glomerular filtration rate (G.F.R.) and blood pressure are shown as means (± standard error) for: normal male and female rats (Controls), rats with diabetes insipidus (after removal of their neurohypophysis), rats that had been adrenalectomized for 4 days and rats with diabetes insipidus and adrenalectomized. All were *loaded with distilled water* by stomach tube at a dosage of 3 $cm^3/100\ cm^2$ surface area. The sodium output is markedly increased by adrenalectomy despite the drop in blood pressure, G.F.R. and urine output (from Chester Jones, 1957*b*).

	NUMBER OF SPECIMENS	URINE ML/100 G/ MIN	NA MICRO-EQ/100 G/ MIN	K MICRO-EQ/100 G/ MIN	G.F.R. ML/100 G/ MIN	BLOOD PRESSURE MM HG
Controls	29	0·036 ±·0014	0·053 ±·0045	0·145 ±·019	0·600 ±·059	108·9 ±2·7
Diabetes insipidus	10	0·034 ±·0025	0·049 ±·0037	0·127 ±·009	0·581 ±·114	96·0 ±2·7
Adrenalectomized	30	0·0037 ±·0005	0·320 ±·053	0·101 ±·012	0·103 ±·016	52·5 ±1·5
Diabetes insipidus and adrenalectomized	12	0·0026 ±·0004	0·314 ±·077	0·097 ±·009	0·112 ±·026	55·9 ±1·3

invertebrates, though it might perhaps be expected in land Crustacea. That claimed for the cockroach, *Blabera*, is an extract which has only been shown to act on rats (Stutinsky, 1953); that claimed for extracts of the post salivary glands of some Cephalopoda has likewise only been tested on unrelated animals (Erspamer and Boretti, 1950).

VERTEBRATA. Increase in the water content of the tissues of vertebrates can be obtained either from the food in the gut, where no hormone action has been found, or from the environment, as when Amphibia move from dry to damp conditions, or back to water. An antidiuretic hormone from the neurohypophysis not only increases skin permeability, to facilitate this water uptake, but also favours water conservation by increasing its reabsorption from the urine in the kidneys and bladder. Its action at all three sites is to increase cell permeability and facilitate water endosmosis.

Such antidiuretic hormones occur in most vertebrates and are closely akin to the so-called "vasopressin" of mammals. Since the main function, even of the latter, is not to control the tonus of blood vessels as its name implies, but to increase reabsorption of water from the urine in the kidneys and thereby reduce the urine flow, "antidiuretin"* would seem to be a more descriptive name for this type of hormone, so often referred to as ADH.

ADH is secreted from the hypothalamus and stored in the neurohypophysis (§ 2.111), whence it is released into the circulation (Table 25, p. 208).

Increase in permeability of the skin

AMPHIBIA. Since the skin of amphibians is moist and its permeability to water can be varied, it plays as important a part in the control of the water balance in these animals as do the kidneys and the bladder. There is no longer thought to be a "water balance principle", distinct from the antidiuretic hormone and acting only on the skin of amphibians; but the amphibian ANTIDIURETIC HORMONE is chemically more akin to oxytocin than to mammalian ADH (= vasopressin). As a rule, frogs do not drink an appreciable amount of water, unless they are immersed in a relatively saline medium; but water losses following exposure to air can quickly be made good, on the animals' return to water, by imbibition through the skin. This can be shown by ligaturing the cloaca of such dehydrated frogs to stop loss of urine; then increase in weight over two or three hours from the time of their return to water will show the amount of water uptake. Comparison with control frogs, which had already been in water for some time, shows that the rate of water uptake after dehydration may be three times greater than in the controls. In the latter, the loss of urine, if the cloaca were not ligatured, would balance this uptake and the weight would remain constant (Fig. 5-20*a*). Removal of the hypophysis decreases, but does not inhibit, the rate of water uptake by dehydrated frogs (Fig. 5-21), presumably because the osmotic gradient is steeper than in the normally hydrated controls. Injection of a neurohypophysial extract (FROG ADH) more than restores the capacity for water uptake (Fig. 5-20*b*). Even isolated skin treated with the same hormone shows an increase in water uptake large enough to account for the changes seen in whole frogs (Fig. 5-20*c*).

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* It should not be confused with "Antidiuretin", a commercial product with a similar action.

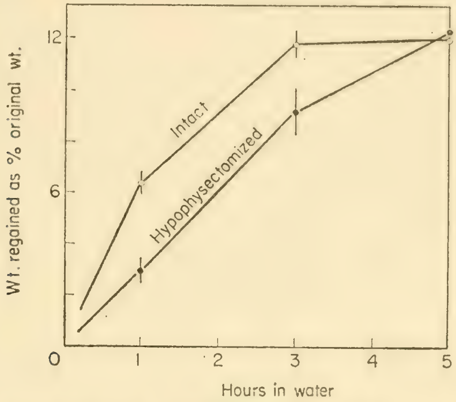

FIG. 5-21 Rates at which normal and hypophysectomized frogs, *Rana pipiens*, return to their initial weight after being dehydrated and then placed in water at time 0. Hypophysectomy and the consequent lack of frog ADH reduces, but does not inhibit, water uptake through the skin (from Levinsky and Sawyer, 1953).

Xenopus, the wholly aquatic clawed toad, shows little increase in water uptake in response to ADH injection; but the terrestrial toad, *Bufo americana*, (though not *Bufo bufo;* Sawyer, 1956) shows a greater increase than the frog. Moreover, the toad is able

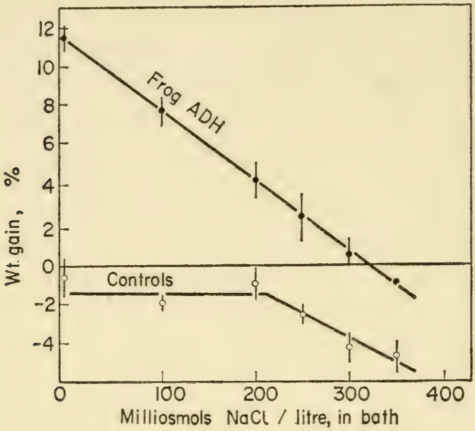

FIG. 5-22. Percentage change in weight of the frog, *Rana*, after immersion for 3 hr each time, in baths of different osmotic concentration. Increase and decrease in weight, due to change in water content, are shown as ordinates above and below the horizontal line; values for osmotic concentration as abscissae range from distilled water, O, to values above that of plasma (*ca.* 325 milliosmols). Control frogs maintain a constant value over much of this range; but frogs that had received 5 units/100 g body weight of NEUROHYPOPHYSIAL EXTRACT (frog ADH) allow a free flow of water through their skin, so that their weight changes steadily until they come each time into osmotic equilibrium with the external medium (from Sawyer, 1951).

to take up water from damp moss and does not need to be submerged like the frog. There therefore seems to be an adaptive correlation between the sensitivity of the skin to the hormone and the degree of adaptation to land life. The neurosecretory material in the neurohypophysis is found to be depleted in dehydrated frogs, indicating that it has been secreted in response to the need to absorb water.

Experimentally the skin of a frog or toad behaves as if it had ultra-microscopic pores that are enlarged by the neurohypophysial hormone to allow an osmotic flow of water, instead of the slower diffusion (Ussing, 1954). The rate of flow is then determined by the osmotic gradient (Fig. 5-22). Even with 1/10th Ringer as the "outside medium" for isolated skin, the net influx of water is several times greater than it could be by diffusion. In fresh water the rate would be still greater.

Ussing supported his "pore theory" by putting thiourea on both sides of the isolated skin; but the thiourea on one side had its carbon, and on the other its sulphur, isotopically labelled, so that the flux could be followed in both directions. When neurohypophysial hormone was present, the increased flux of thiourea was much greater than the increase in flux of the water. It may be assumed that the hormone dilates pores that are normally too small for molecules of thiourea, though just large enough for water. Moreover, "the influx of thiourea is more rapid than the outflux, even when the concentration is the same on both sides", and this reflects the fact that thiourea is swept through the pores in the osmotic flow of water (Sawyer, 1957).

Increase in permeability of the bladder

Amphibia. Reabsorption of water from the bladder in *Rana* is similar to that from the skin and kidney tubules and responds in like manner to frog ADH injections and to dehydration, a state which presumably stimulates the secretion of the frog's own neurohypophysial hormone (Fig. 5-24).

Mammalia. There is no evidence of water being reabsorbed from the bladder in mammals.

Increase in permeability of the kidney tubules

Amphibia. When amphibians are exposed to dehydrating conditions, conservation of water in the kidneys is stimulated by the independent action of antidiuretin at two points, the glomerulus and the tubule.

The glomerular filtration rate (G.F.R.) is determined by the arterial blood pressure, the resulting filtrate being isosmotic with the blood plasma and only differing from it in the lack of proteins or other colloids. The top curve (C_{CR}) in Fig. 5-23 shows the effect of the pressor action of frog ADH in reducing the volume of the filtrate by constricting the blood flow to the glomerulus. It can also reduce the number of glomeruli which are active. After injection of antidiuretin the kidney tubules, therefore, receive a reduced volume of isosmotic filtrate, containing salts, sugar and urea.

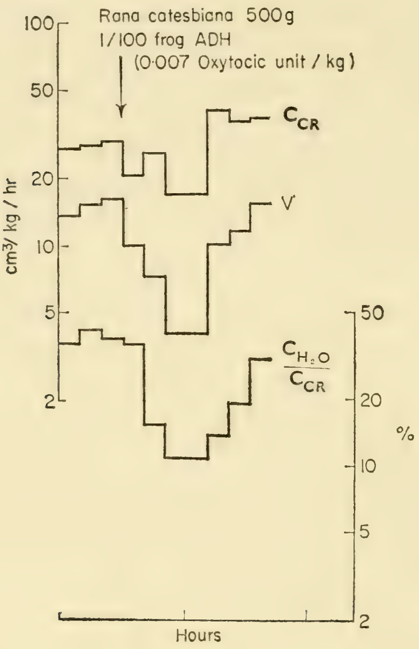

FIG. 5-23. Responses of the bullfrog, *Rana catesbiana*, during 2 hr after an injection of the ANTIDIURETIC HORMONE from the NEUROHYPOPHYSIS. Frog ADH reduces G.F.R., the filtration rate (shown by creatinine clearance, C_{CR}, on ordinate scale on left) but not sufficiently to account for the large reduction in volume (V on same scale) of excreted urine. This is chiefly due to the reduction in the ratio (shown as $\frac{C_{H_2O}}{C_{CR}}$ on percentage scale on right) of clearance of "free water" to that of creatinine, due to reabsorption of water in the kidney tubules. Control injections caused no significant changes (from Sawyer, 1957).

In the tubules all the sugar is reabsorbed, but the urea, to which the tubules are impermeable, is excreted. Monovalent salts, which account for much of the osmotic pressure of the filtrate, are less actively reabsorbed in the tubules during antidiuresis than during diuresis (§ 5.312 and Fig. 5-15*b*, p. 214).

The action of ADH on the tubules is to increase their permeability, presumably by increase in pore size, as in the skin. The obligatory endosmotic flow of water then follows closely on the active inward movement of salts, so that the final urine tends to be isosmotic with the plasma. The reduction in clearance of "free water" is shown in the lowest curve (Fig. 5-23) to be much greater than could be accounted for by the reduction in glomerular filtration rate alone, as shown by the creatinine clearance. It is therefore assumed that the reduction in volume of urine (V, Fig. 5-23) is mainly due to reabsorption of water because of the increase in tubule permeability, and not only to the reduced G.F.R.

No Amphibia have been found to excrete urine more concentrated than that which is isosmotic with the plasma. There is, therefore, no need to postulate for them any seat of active transport of water from the kidneys to the tissues.

There is considerable specific variation among Amphibia in their sensitivity to their own ADH. Removal of the neurohypophysis, and therefore of the store of this hormone, has no effect in *Bufo bufo* and *Rana temporaria*, as compared with intact controls. *Bufo arenarum*, when kept out of water, behaves like *R. catesbiana* (Fig. 5-23). *Bufo marinus* of South America may be even more sensitive than these to frog ADH; in hydrated and hypophysectomized specimens only about 35 per cent of the filtered water was reabsorbed by the tubules; but after injecting extracts containing frog ADH this rose to an average of 65 per cent (Sawyer, 1956).

The rate of secretion of antidiuretin from the neurohypophysis in Amphibia may well be mediated through osmo-receptors in contact with some of the main arteries, as it is in mammals (Chester Jones, 1957*a*).

TELEOSTEI. In sea water the body fluids of teleosts are maintained at a level considerably hypotonic to the medium by drinking sea water and excreting the excess salts through the gills. Kidney excretion is reduced to a minimum, largely by a loss of glomeruli, though the action of an antidiuretic hormone might also be expected. Although extracts of the fish neurohypophysis have a potent antidiuretic effect on frogs, there is no direct evidence of the hormone having the same action on the fish themselves. The best indirect evidence for the relation of hormones to an antidiuretic function in *Callionymus* and *Ammodytes* (Arvy, 1957; Arvy, Fontaine and Gabe, 1954) is the observation that on transfer from normal sea water to hypertonic sea water, the increased dehydrating action of the environment is accompanied by depletion of the neurosecretory store in the hypothalamus and NEUROHYPOPHYSIS. The secretion is re-formed when the fish are restored to normal sea water and increased if they are placed for a short

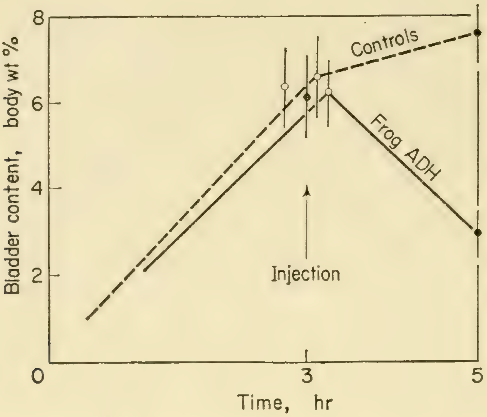

FIG. 5-24. Effects of injection of NEUROHYPOPHYSIAL EXTRACT (Frog ADH), at the time marked by the arrow, on the water content of the frog, *Rana pipiens*. ○ : values calculated from changes in body weight; ● : values for direct measurement of bladder contents. The cloaca was ligatured and injected with phenol red to show if any leakage occurred; the frogs then sat in water, which was imbibed through the skin and excreted into the bladder, for 3 hr; then the controls (dotted line) continued to excrete for the next 2 hr while the specimens, which received the injection at hour 3 (full line), showed a marked decrease in bladder water. This was taken to mean that water had been reabsorbed into the tissues from either the bladder or the cloaca (from Sawyer, 1956).

time in hypotonic sea water, where the tissues would tend to become over-hydrated and there would be no call for the secretion of an antidiuretic hormone. Presumably in normal sea water the supply of the hormone is in balance with the demand and no histological change is observable.

Reptilia. Little seems to be known of water control in reptiles. Chester Jones (1957*a*) writes: "Many reptiles are adapted to arid conditions and even those whose habitat is in or near water have no movement of water through the skin . . . nor is the reptilian renal tubule specifically adapted for water reabsorption beyond the plasma osmotic concentration. The alligator is very responsive to the antidiuretic effect of . . . pitressin [mammalian ADH] rather than the pitocin fraction, as in frogs. Antidiuresis is effected, at least partly, by lowering the glomerular filtration rate, pitressin [contracting] the smooth muscle of the afferent glomerular arteriole." Metabolic waste products and especially the uric acid are eliminated not only by glomerular filtration, but probably to a much greater extent by tubular secretion.

Aves. Even less seems to be known of birds, but they are probably similar to reptiles.

Mammalia. The hormone control of water balance in mammals has been most fully investigated in rats, but seems to be basically similar in other forms, including the dog. In one way the situation is simpler than in the frog because the skin is practically waterproof, and the supply of water is, therefore, derived entirely from the gut contents by intestinal absorption, where no hormonal influence has been detected. The loss of water from the sweat glands does not appear as a rule to be under hormone control either (§ 4.14); nor does the loss through the lungs. The main control of the water balance occurs in the kidneys, but it is only partially dependent on hormones, because mammals have, in addition to the systems found in the frog, the "concentrating mechanism" already mentioned (§ 5.321).

If the antidiuretic hormone, ADH, were to have the same effect in mammals as in the frog it would increase the permeability of the distal kidney tubules and allow of water reabsorption there until the urine became isosmotic with the plasma (Fig. 5-15*b*, p. 214). It is clearly of importance for wholly terrestrial mammals to be able to conserve more water than this, and in fact it is commonly found that the urine is markedly hypertonic. Recent evidence shows that in addition to the action of an antidiuretic hormone (ADH injected as vasopressin in graded doses in Fig. 5-25) there is a process of active reabsorption of water. Although the exact means by which it is brought about is still under discussion (e.g. Wirz, 1957 and Sawyer, 1957), it is clear that it is independent of hormone control. This has been demonstrated in water-loaded dogs, in which urine flow is maximal and antidiuretin, ADH, is therefore not being secreted (Berliner and Davidson, 1957). Acute unilateral reduction of G.F.R., induced by occluding the blood supply to one kidney only, so reduces the volume of the filtrate reaching the "concentrating mechanism" of that side, that the urine collected separately from the two ureters becomes

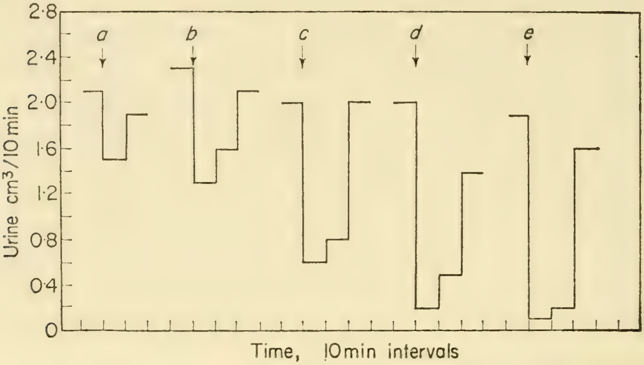

FIG. 5-25. Urine output (ordinates) of an unanaesthetized rat, *Rattus*, after being given a standard water load by stomach pump (5 % body weight, or *ca.* 11·3g) and then a dose of ANTIDIURETIC HORMONE (vasopressin). Successive doses were given intravenously, in the order *b*, *c*, *d*, *a*, *e*, at the times marked by arrows and were graded: *a* = 100, *b* = 200, *c* = 400, *d* = 600, *e* = 800 μ units. The antidiuretic effect, shown by the drop in urine output, approaches a maximum after dose *d*, and the further increase in hormone given at *e* has practically no greater effect. The method can be adapted for assaying antidiuretic substances over the lower range of concentrations (from Ginsburg and Heller, 1953).

hypertonic on the treated side, while remaining iso- or even hypotonic on the other side.

This concentration may or may not be limited to the collecting ducts rather than occurring in the renal tubules (Fig. 5-15). It is certainly limited to a maximal rate of water uptake, no matter what volume of fluid is delivered to it from the tubules; it is also limited to a maximal osmotic concentration of the urine, relative to, but considerably above, that of the plasma. "The degree of urinary concentration in the mammal is determined . . . largely by the volume of water delivered to this concentrating mechanism" (Sawyer, 1957).

The natural secretion of the antidiuretic hormone can be brought about by stimulation of osmo-receptors in the anterior hypothalamus of the brain, a region supplied by branches from the internal carotid arteries. It has been shown in dogs that infusing these branches of the carotids for about half an hour with sufficient saline to increase the osmotic pressure of the blood by some 2 per cent can reduce the urine flow by 90 per cent. This treatment is much more effective than giving similar saline infusions elsewhere in the circulation (Jewell and Verney, 1957). The presence of the saline presumably has the same effect as tissue dehydration; yet it can be shown that although ADH injection into an isolated heart-lung preparation causes antidiuresis it does not reduce the G.F.R., whereas natural dehydration does both. The factor controlling G.F.R. in mammals is not known, since recent work all points to the vascular constrictor, "vasopressin", being one and the same hormone as ADH.

Haemorrhage also stimulates secretion of ADH, possibly by affecting vagal nerve endings sensitive to hydrostatic pressure in the heart or the great veins (Heller, 1956).

Sawyer (1957) wrote: "Diuresis and antidiuresis can . . . be explained in the mammal simply in terms of an increase in permeability of the distal segment to water under the influence of the antidiuretic hormone. This increase in permeability, since it involves reabsorption of water only up to the isosmotic state, could be interpreted in terms of a change in pore size, as the evidence indicates to be the case in the [frog] skin, and as we have inferred to be the case in the frog bladder" and kidney. But this statement was made prior to the publication of Chester Jones's evidence, referred to above, showing the importance of cortical hormones in causing water diuresis.

5.4 Balance of calcium and phosphates

Unlike water and the monovalent electrolytes, calcium and phosphates are of more importance in growth than in the direct relation of the animal to its environment. The changes in their concentration in the blood are, therefore, slower and less spectacular, and fewer observations seem to have been made upon them.

Arthropoda. Despite the differences in the metabolic significance of the control of calcium and phosphates, as compared with the salts previously considered, the hormones concerned in their control seem, nevertheless, to be derived from the same organs, namely the Y-organ and eyestalk in the Crustacea (p. 222) but not in the Insecta. In both classes, the changes in calcium and phosphates are associated with moulting, since in these forms with hard exoskeletons it is necessary for one or both salts to be withdrawn from the old skin before it is shed. During this phase they appear in the blood and rise to a maximum at the time of the moult, and then decrease suddenly as they are re-incorporated into the new shell, together maybe with fresh calcium rapidly absorbed from outside sources. The changes are more marked in Crustacea, which have heavily calcified shells, than in Insecta, where such structures are unknown and would clearly be too heavy to permit flight in air.

Vertebrata. Since vertebrate growth is a continuous process and not as a rule accompanied by moulting, the changes in calcium and phosphates are more gradual; but the accumulation of these salts is an essential preparation for their deposition in bone in the later stages of growth.

For convenience in recording what evidence has so far been put forward on the action of hormones on these salts, their concentration in the blood will be used as the indicator.

5.41 BALANCE OF CALCIUM

5.411 *Increase of calcium in the blood*

Crustacea. In *Carcinus*, a single injection of an extract of the Y-organ, that contains the moult-promoting hormone, MPH,

TABLE 28. METABOLIC HORMONES CONTROLLING THE BALANCE OF CALCIUM AND PHOSPHATES

EFFECT	VERTEBRATE		INVERTEBRATE	
	ORGAN OR HORMONE	EXAMPLE	ORGAN OR HORMONE	EXAMPLE
5.41 CALCIUM BALANCE	Ultimobranchial body	*Astyanax*	Y-Organ	*Carcinus*
5.411 *Increase of* Ca *in blood*	Parathyroid	Amphibia Aves Mammalia		
	Pars tuberalis ?	*Xenopus*		
5.412 *Decrease of* Ca *in blood*	Neurohypophysis ?	*Xenopus*	Ganglionic-X-organ and Sinus gland	*Astacus*
	Adrenal cortex	*Oryctolagus* *Canis*		
5.42 PHOSPHATE BALANCE				
5.421 *Increase of* P *in blood*	Adrenal cortex	Mammalia	Y-Organ ?	*Panulirus*
	Thyroid	,,	Corpora allata	*Carausius*
5.422 *Decrease of* P *in blood* (increased excretion)	Ultimobranchial body	*Astyanax*	Ganglionic-X-organ and Sinus gland ?	Decapoda
	Parathyroid	*Rattus* *Canis*	Prothoracic gland	*Carausius*

causes a fourfold rise in blood calcium lasting about 5 days (Fig. 5-26). The effect has been obtained in old crabs which would not have moulted again (terminal anecdysis, Carlisle, 1957), and is followed by moulting within a few weeks, if injections are repeated. The same hormone appears to be responsible for moulting and for Ca increase. This accounts for the earlier observations on many decapods, such as *Crangon*, *Panulirus*, *Astacus*, *Carcinus* and *Uca*, that removal of the eyestalks increases the blood calcium; for the eyestalks contain a hormone which inhibits the action of the Y-organ that lies within the head capsule. Increased blood calcium leads to the formation of calcareous gastroliths, which serve as stores of calcium and normally show a diurnal rhythm in their rate

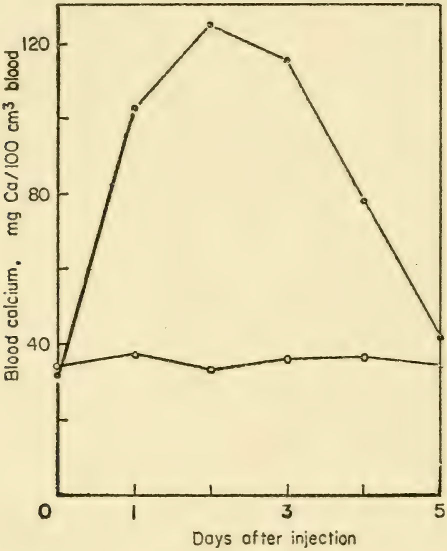

FIG. 5-26. Effects of an injection of an extract of Y-ORGAN of the crab, *Carcinus*, on the level of the blood calcium (ordinates) in the same species, during the succeeding 5 days (abscissae). Black circles show the effect on specimens in terminal anecdysis, when they no longer moult naturally and do not secrete any hormone from their own Y-organ. Open circles (below) show the lack of effect of an extract of leg nerve on similar specimens (from Carlisle, 1957).

of formation in the premoult period. This could be due to diurnal fluctuations in hormone secretion.

There is some evidence that the secretion of the Y-organ is under the endocrinokinetic control of Hanström's sensory pore organ (§ 4.211).

INSECTA. There appears to be no evidence about hormonal control of changes in the level of calcium in the blood of insects.

VERTEBRATA. Increase of calcium in the blood of vertebrates is usually attributed to the hormone of the PARATHYROIDS or their equivalent structures, the ULTIMOBRANCHIAL BODIES of teleost fish. The hypophysis has been shown to play a part in calcium control that is neither consistent nor clearly understood; but most recent evidence seems to be against the view once held, that it supplies an endocrinokinetic hormone for the parathyroids. It is more probable that its action, at least in mammals, is indirect, through secretion of thyrotrophin, TSH, that stimulates the thyroid glands to secrete thyroxine (§ 4.221). This results in an increase in blood phosphates, of which a high concentration stimulates the parathyroid glands to secrete their PARATHORMONE (§ 2.221).

TELEOSTEI. The ULTIMOBRANCHIAL BODIES of teleost fish are embryologically comparable to the parathyroids of tetrapods; but their physiological similarity has only recently received any support and is still not fully proved. Like the parathyroids their hypertrophy and histological activity is associated with decalcification of the skeleton and the deposition of calcareous stones (renal calculi) in the kidneys (Rasquin and Rosenbloom, 1954). It may be supposed that this coincides with an increase in the calcium content of the blood, as it would in mammals; but this has not been measured in fish in relation to ultimobranchial activity.

The hypophysis is also thought to have an effect upon the calcium metabolism; but the evidence so far seems to be rather inconsistent. In the eel, *Anguilla*, direct measurement of the serum calcium showed it to vary by 10 per cent in controls, but to drop by as much as 28 per cent in 10 days after hypophysectomy (Fontaine, 1956). On the other hand, *Astyanax* and *Fundulus* react in the opposite way, so that reduction in calcification of the skeleton and formation of renal calculi are both associated with reduction or loss of the hypophysis, and presumably therefore with an increase of serum-calcium (G. Pickford, 1954). In *Astyanax*, inactivity of the hypophysis resulted from maintaining the fish in darkness for over 60 weeks and was associated with hypertrophy of the ultimobranchial bodies (Rasquin and Rosenbloom, 1954). The last example seems to be definite, even if it is thought that the evidence from hypophysectomized *Fundulus* is not strong because few fish were used, and these were apparently rather abnormal in losing their ability to stand transfer to fresh water after the operation. Hypophysectomy does not necessarily have the latter effect upon *Fundulus* (Fontaine, 1956).

This association of active ultimobranchial bodies with an inactive hypophysis is the reverse of the situation in mammals, where the presence of TSH from an active hypophysis stimulates parathyroid activity and increases blood calcium, as in the eel; albeit the effect is indirectly mediated through the thyroids and their power of increasing phosphates in the blood. It is possible that these contradictory results may have been due to technical difficulties, or to morphological differences in the hypophyses of the three genera of fish concerned; possibly the hypothalamus was injured, or all parts of the hypophysis were not removed in all cases (G. Pickford and Atz, 1957). Alternatively, it has been postulated that the effect upon the ultimobranchial tissue may be indirectly due to a hormone, ACH, of the adrenal cortex causing an increase in serum phosphates (§ 5.421). ACH appears to be secreted for some time in *Astyanax* in the absence of adrenocorticotrophin, ACTH (§ 4.231).

AMPHIBIA. The most definite evidence for hormone control of calcium in Amphibia is that complete removal of the PARATHYROID glands from the bullfrog, *Rana catesbiana*, is followed by a fall in blood calcium and eventual death from muscular tetany, much as in mammals. Injections of parathyroid extract (parathormone) prolonged the life of some of the frogs (Waggener, 1930). The African clawed toad, *Xenopus*, shows seasonal variations in serum calcium, the level being highest when daylight is longest; but it has only been assumed, without evidence in this case, that the parathyroids are active when the calcium is increased.

It has been suggested that this seasonal control of calcium may be mediated through the hypophysis in somewhat the same way as seasonal effects upon ovary maturation (Zwarenstein and Shapiro, 1933), since the two are correlated in time; but the evidence on the rôle of hypophysial hormones is almost as obscure here as it is in fish.

TABLE 29. EFFECT ON BLOOD CALCIUM OF INJECTION OF HYPOPHYSIAL HORMONES INTO *XENOPUS*

NORMAL	COMPLETELY HYPOPHYSECTOMIZED		
Control in captivity	Uninjected control	Injected with Antuitrin*	Injected with Pituitrin*
10·4	7·6	8·6	6·8
8·2	7·4	9·0	6·4
8·0	8·2	8·4	6·8
8·6	7·6	9·4	6·6
9·2	6·5	—	6·6
10·0	7·6	—	5·8
9·4	7·3	—	—
8·2	6·8	—	—
Mean 9·0	7·4	8·9	6·5 mg %

Injections of histamine had no effect on the calcium content of serum measured to within 0·4 mg % (from Shapiro and Zwarenstein, 1933).

* 1 cm^3 each of Parke Davis preparations. As these were mammalian extracts, the Antuitrin would contain ACTH and TSH, of which the latter could exert an indirect effect (see text). The Pituitrin would contain ADH but probably no intermedin, though possibly ACTH contamination.

It has been claimed that the hypophysis can secrete two hormones with opposing actions upon the serum calcium; that from the PARS TUBERALIS of the hypophysis (§ 2.112) increasing the calcium, and that from the neurohypophysis decreasing it slightly (Shapiro and Zwarenstein, 1933). The structure of the pituitary body of *Xenopus* is such that its parts can be readily separated and, after removal of most of it, the pars tuberalis alone will regenerate;

its presence can then be detected by its secretion of the melanophore concentrating hormone (§ 3.223), and the increase in blood calcium. Moreover, in completely hypophysectomized toads injection of mammalian "Antuitrin" (containing TSH, among other hormones) from the anterior lobe causes a rise in blood calcium, while injection of "Pituitrin" from the posterior lobe causes a decrease (Table 29). There appears to be no exact parallel for the latter effect in other vertebrates; but dilution of calcium ions in the blood, as a result of the action of an antidiuretic fraction in the Pituitrin, causing increased water retention (§ 5.32), does not seem to have been considered.

AVES. Diffusible serum calcium in some birds has been found to rise to double its normal value just before ovulation, and to fall again afterwards. The calcium is thus made available for eggshell formation, and its release into the blood is believed to be due to secretion of hormone from the PARATHYROID GLANDS, which show correlated histological signs of secretory activity but have not been fully tested physiologically. Parathyroidectomy resulted in lowered Ca in the blood and premature laying of eggs with less Ca in the shell. This was only achieved if the birds did not die from the lowering of Ca in the blood, which normally stimulates parathormone secretion (Polin and Sturkie, 1957). As in the fish, darkness also stimulates parathyroid activity; but its damaging effect on the skeleton can be ameliorated by treatment with either vitamin D or ultra-violet light.

MAMMALIA. "The most striking and conspicuous result of the subcutaneous injection of a potent PARATHYROID extract in a normal dog is the rise in the serum calcium. The amount of this rise is in general proportional to the dose, except that rises above 18 mg per cent are seldom observed; the rise attains its maximum in 12 to 18 hours."

"Extirpation of the parathyroid glands of the dog leads usually within 2 or 3 days to characteristic . . . tetany. There is a prompt and rapid fall in the concentration of calcium in the serum . . . [and] death finally results from exhaustion or from asphyxia due to respiratory spasm" (Thomson and Collip, 1932; Fig. 5-27). This effect can be reversed in the early stages by injecting PARATHORMONE. After parathyroidectomy, the bodies of rats contain more calcium and phosphate than do the controls, the excess being in the muscles rather than in the bones. Excess parathyroid secretion, or injection, usually results in maintaining high serum calcium and a high level of Ca excretion at the expense of the calcification of bone (Bartter, 1954).

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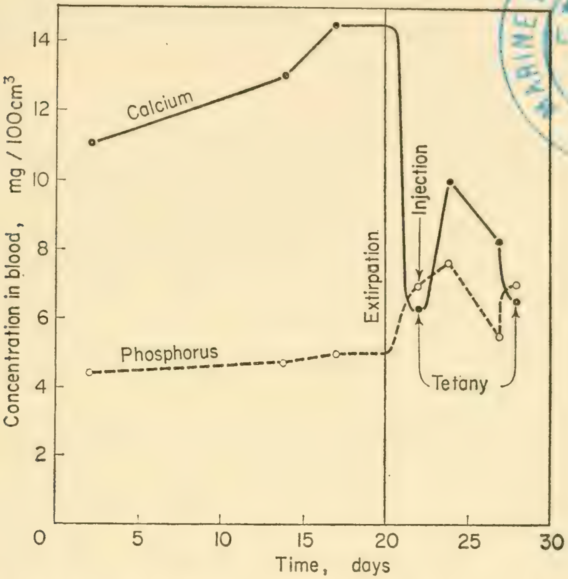

FIG. 5-27. Changes in the concentrations of calcium and inorganic phosphates in the blood of the dog, *Canis*. They change little prior to extirpation of the parathyroid glands on day 20, when phosphates rise and calcium drops sufficiently to induce tetany. Injection of PARATHORMONE raises the calcium value sufficiently to prevent the return of tetany for about a week; but tetany occurs whenever the calcium level falls below about 7 mg/100 ml in the blood (from Weaver and Reed in Winton and Bayliss, 1955).

5.412 *Decrease of calcium in the blood*

CRUSTACEA. The weight of evidence favours the assumption that the GANGLIONIC-X-ORGAN/SINUS GLAND complex is the source of a hormone which restrains the rate of calcium accumulation in the blood; it may be the same hormone as MIH that restrains the moulting rate at the same time. Most of the evidence is indirect and derived from observations on sinus gland and eyestalk removal; but in *Cambarus* (Scudamore, 1947) injections of sinus gland extract result in a decrease in the level of blood calcium, after it has been raised by eyestalk removal. The level does not return to normal; but different dosage levels have not been tested.

Removing the sinus gland only, as compared with removing the whole eyestalk in *Astacus*, has the results on the level of blood calcium shown in Table 30.

TABLE 30. CHANGES IN THE CALCIUM CONTENT OF THE BLOOD OF THE CRAYFISH (*ASTACUS*), FOLLOWING REMOVAL OF EITHER THE SINUS GLANDS OR THE WHOLE EYESTALKS

Values for Ca in mg % (from figures given by Havel and Kleinholz, 1951).

DAYS AFTER OPERATION	CONTROL	WITHOUT SINUS GLANDS	WITHOUT EYESTALKS
1 to 9	55	34	lowered
10 to 30	—	50	52
39	—	50	65
54	—	50	116
47 to 62	no moult	no moult	moult
Moult-inhibiting-hormone, MIH	present	present	absent

This shows that some structure in the eyestalk, other than the sinus gland, can produce the CALCIUM-DECREASING HORMONE. It is presumably the ganglionic-X-organ, which is the usual source of the hormone stored in the sinus gland, but it has not been located for certain (Havel and Kleinholz, 1951).

AMPHIBIA. As mentioned above, a hormone from the neurohypophysis is said to decrease the serum calcium in *Xenopus*, when injected as Pituitrin into completely hypophysectomized toads (Table 29; Shapiro and Zwarenstein, 1933).

MAMMALIA. It has been claimed (e.g., Thomson and Collip, 1932) that a hormone from the ADRENAL CORTEX can lower the level of serum calcium in the rabbit; but these animals appear to be particularly bad subjects for experiments on control of blood calcium, owing to their variable responses. Conversely, however, adrenalectomy raises the serum calcium in dogs.

5.42 BALANCE OF PHOSPHATES

There is a characteristic difference in the control of phosphates in Crustacea and Vertebrata. In the former, the phosphate concentration in the blood changes in the same sense as does that of calcium, and both are related to stages in moulting. In vertebrates the changes in phosphates and calcium in the blood usually respond to the same hormones, but do so in the opposite sense, phosphates being decreased for instance when calcium is increased.

The level of phosphates in the blood may, however, be a bad indicator of the action of hormones on phosphate metabolism, since the blood may be charged with phosphates as a result of either protein catabolism or resorption of calcium phosphates from vertebrate bone, and may be depleted either by excretion or by protein synthesis in the tissues.

5.421 *Increase of phosphates in the blood*

CRUSTACEA. Changes of phosphates in the blood are usually similar to those of calcium; but it appears that at least the threshold values at which the controlling hormones become effective may be different. For instance, in *Panulirus* (Travis, 1951), eyestalk removal can decrease the phosphate content of the hepatopancreas (and presumably increase the content of the blood) without affecting the level of calcium; in most Decapoda, however, eyestalk removal increases the level of both phosphates and calcium in the blood. There is no direct evidence for the intervention of a hormone from the Y-ORGAN in the increase of phosphates in the blood, as there is for calcium, nor that this is released from inhibition by eyestalk removal (§ 5.411); but it may perhaps be assumed to be active here also.

INSECTA. The secretion of the CORPORA ALLATA stimulates the anabolism of such organic phosphates as the mono- and di-phosphoric hexose esters, which are not formed in its absence. This metabolism-stimulating function may be compared with the increase in oxygen consumption caused by the same hormone in *Calliphora* and elsewhere among insects (§ 5.111). It is a rather different type of reaction from the translocation of phosphates associated with calcium in crustaceans and vertebrates, nor is there apparently any such calcium change in insects.

Removing the corpora allata from developmental stages of *Carausius* results in a decrease in the organic phosphates in both the blood and the tissues relative to mineral phosphates (L'Hélias, 1954). The difference between allatectomized and control specimens is greatest in the 5th intermoult period and is least in the "adultoid" stage, after the 7th moult, when the corpora allata might be expected to be inactive in the controls (cf. Part II, § 3).

VERTEBRATA. There appears to be no clear-cut evidence on the action of any hormone that increases blood phosphates, except in mammals. Rasquin and Rosenbloom (1954) have discussed the possibility of cortical control in fish, but have brought forward no direct evidence for it (§ 5.411).

MAMMALIA. It appears from experiments on rats that THYROXINE causes a direct increase in the level of phosphates in the blood. The action is masked to some extent in both intact and thyroidectomized controls, since the rise in phosphates induced by thyroxine injection quickly stimulates secretion by the parathyroids, and the phosphate level is thereby restored to normal (Engfeldt and Hjerquist, 1952). The action of the ADRENAL CORTEX, when stimulating protein catabolism, also increases P as well as N in the blood, at least until the balance is restored by the resulting increase in parathormone secretion (§ 5.422). The opposing claim, that injections of a cortisone-like hormone of the adrenal cortex can lower the maximal amount of phosphate ions reabsorbed by the kidney tubules (Roberts and Pitts, 1953) and can increase the amount excreted, is probably therefore based on observations of an indirect effect, due to the stimulation of the parathyroids.

5.422 *Decrease of phosphates in the blood*

CRUSTACEA. Since eyestalk removal appears to increase the phosphate content of the blood of Decapoda, it may perhaps be assumed that a hormone of the GANGLIONIC-X-ORGAN/SINUS GLAND complex is normally responsible for decrease or restraint in the level of blood phosphates, as it is for protein catabolism (§ 5.221); but there is little quantitative data on this. The action might be indirect through inhibition of Y-organ secretion (§ 5.411).

INSECTA. The most marked decrease of total phosphates in the blood of *Carausius* occurs at the time of the 5th and 6th nymphal moults and of the final moult to the adult (L'Hélias, 1954). This may be compared with the decrease in blood-sugars which occurs at the same times, when the MOULT-PROMOTING HORMONE, ECDYSONE, is being actively secreted by the prothoracic gland (§ 5.212). There is no direct evidence of hormonal control of total phosphates in the blood; but the source of ecdysone was left intact in both the controls and the allatectomized specimens used in these experiments (§ 51.42), and both showed phosphate decreases whenever they moulted.*

TELEOSTEI. The ULTIMOBRANCHIAL BODY of *Astyanax* is thought to be the homologue of the tetrapod parathyroid gland. It is stimulated by the increase of phosphates in the blood and it has therefore been assumed that its normal action is also the same as that of the parathyroids, namely to decrease the level of phosphates in the blood by increasing their excretion (Rasquin and Rosenbloom, 1954).

MAMMALIA. A decrease in phosphates in the blood, shown chiefly by the inorganic fraction, results from injecting PARATHYROID extracts; but it seems that this may be due to at least two causes: increased transfer of P from the blood to the tissues, and increase in the so-called phosphate diuresis. Since this increased phosphate excretion is not just proportional to the level of phosphates in the blood, but increases more rapidly than the increment of P in the glomerular filtrate, it is postulated that PARATHORMONE, the secretion of which is stimulated by a high phosphate level in the blood, actively decreases phosphate reabsorption in the kidney tubules (Bartter, 1954).

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* Moults are reported as normal. No mention is made of any premature metamorphosis in those specimens from which the corpora allata had been removed (cf. Part II, § 3).

The initial effect of parathormone injection may, however, be an increase in blood phosphates, because, in addition to its effect on excretion, the hormone also facilitates the transfer of phosphates with calcium from the skeleton to the blood stream.

A balance is normally maintained in the blood by a feed-back system, as in the case of insulin (§ 5.212), whereby any decrease in concentration of P in the blood induces a decrease in the secretion of parathormone, while a rise in P causes a rise in parathormone. If the high level in the blood is maintained, the parathyroid gland may even become hypertrophied (Engfeldt and Hjerquist, 1952). There is no sound evidence for any endocrinokinetic control of the secretion of the parathyroid (§ 5.521).

5.5 General considerations

5.51 CHARACTERISTICS OF THE METABOLIC HORMONES

In one respect the metabolic hormones reviewed in this chapter are like some kinetic hormones; wherever they have been most thoroughly investigated, a pair of hormones has been found; they may be synergistic, like glucagon and insulin that between them control the balance of sugar in the blood (§ 5.21), or antagonistic, like the cortical and neurohypophysial hormones which between them determine its salt concentration (§ 5.3). In a somewhat similar way, the moult-promoting and moult-inhibiting hormones of Crustacea may between them control the protein metabolism; but this is not yet fully elucidated, nor is the function of the eye-stalk tip established (§ 5.22). It seems possible that in some cases where, as yet, only one hormone has been determined, an antagonist still awaits discovery. Such might be an antidiabetogenic or an antidiuretic hormone for Crustacea, or a hormone facilitating protein synthesis in vertebrates. Equally promising might be the search in invertebrates for hormones akin to those now known to control the active transport of Na^+ and Cl^- ions in vertebrates (§ 5.31). It is clear from the tables that much more information is needed for cold-blooded vertebrates and even for birds, the study of which is still far behind that of mammals.

Although the present survey has been kept intentionally brief, it still makes clear that the situation is far from simple, even within single classes of vertebrates. It is no longer possible to generalize about even so closely related an order of mammals as the carnivores; for the ferret differs sharply from dogs and cats, and yet resembles rats and man, in secreting its diabetogenic hormone from the adrenal cortex instead of from the pancreas (§ 5.211).

The mode of action of metabolic hormones involves problems of biochemistry outside the scope of the present volume; but the discovery that the stereochemistry of sugar molecules can affect their responsiveness to insulin is a notable advance in this field (§ 5.212).

The long-term nature of their actions distinguishes most metabolic hormones from the quick-acting kinetic hormones, and relates them in nature as well as in function to the morphogenetic hormones (Part II). In fact, there is an obvious overlap between them, since for instance the supply of sugar to the tissues and the stimulation of protein synthesis are essential precursors of growth, and are often controlled by the same hormones.

5.52 CONTROL OF THE SECRETION OF METABOLIC HORMONES

The three ways in which hormone secretion can be controlled are all to be found acting upon different examples of metabolic hormones (Table 31).

5.521 *Direct control of endocrine glands*

Direct control by physical or chemical means, other than nerve impulses or hormones, has been seen already in the case of the kinetic hormones of the vertebrate gut. One of the clearest examples was secretin, the production of which is stimulated by the presence of acid in the gut; it then induces a flow of bicarbonate into the gut until the acid is neutralized (§ 4.111). Similarly the secretion of both the antidiabetogenic hormone, insulin, and the diabetogenic hormone, glucagon, is brought about by the sugars in the blood. A high concentration of glucose stimulates the insulin secretion,

TABLE 31. MEANS OF CONTROLLING THE

SOURCE OF HORMONE	NAME AND/OR ACTION OF HORMONE	MEANS OF CONTROL	KIND OF CONTROL†	SECTION NO.
5.521 *Direct control of endocrine glands*				
Vertebrata				
Islets of pancreas	Insulin, antidiabetogenic	high blood sugar	+	5.212
,, ,,	Glucagon, diabetogenic	low blood sugar	+	5.211
Parathyroids	Parathormone, decrease of P in the blood	high blood phosphates	+	5.422
5.522 *Nervous control of neurosecretory cells*				
Crustacea				
Brain	Respiratory accelerator	nerve	?	5.111
Sinus gland	Respiratory inhibitor	nerve	?	5.112
,, ,,	Diabetogenic	nerve	+	5.211
,, ,,	MIH, decrease of protein catabolism	nerve	—	5.221
,, ,,	Diuretic	nerve	—	5.321
,, ,,	MIH, decrease of Ca in blood	nerve	—	5.412
,, ,,	MIH, decrease of P in blood	nerve	—	5.422
Insecta				
Brain (and/or corpus allatum)	Increase of protein synthesis	nerve	?	5.222
,, ,,	Diuretic	nerve	+	5.321
Suboesoph: ganglion	Diapause	nerve	—	5.112
Vertebrata				
Neurohypophysis	ADH	nerve	+	5.322
,, ,,	Oxytocin	nerve	+ ?	5.312
5.523 *Hormonal control of endocrine glands*				
Crustacea				
* Y-organ	MPH, inhibition of protein catabolism	Hanström's sensory pore organ	+ ?	5.221
,,	MPH, increase of Ca in blood	Hanström's sensory pore organ	+ ?	5.411

SECRETION OF METABOLIC HORMONES

SOURCE OF HORMONE	NAME AND/OR ACTION OF HORMONE	MEANS OF CONTROL	KIND OF CONTROL†	SECTION NO.
Insecta				
*Prothoracic gland	Ecdysone, anti-diabetogenic	brain	+	5.212
,,	Ecdysone, decrease of P in blood	brain	+	5.422
*Corpus allatum	Respiratory accelerator	median neurosecretory cells in brain	— ?	5.111
,, ,,	Respiratory accelerator	nerve	+ ?	5.111
,, ,,	Fat translocation	brain	?	5.121
,, ,,	Diabetogenic	brain	?	5.211
,, ,,	Increase of protein synthesis	brain	?	5.222
,, ,,	Increase of P in blood	brain	?	5.421
Vertebrata				
Islets of pancreas	Glucagon, diabetogenic	adenohypophysis, STH	+	5.211
*Thyroid	Thyroxine, respiratory accelerator	adenohypophysis, TSH	+	5.111
,,	Thyroxine, increase of P in blood	adenohypophysis, TSH	+	5.421
Adrenal cortex	Hydrocortisone, diabetogenic	adenohypophysis, ACTH	+	5.211
,, ,,	Hydrocortisone, diuretic	adenohypophysis, ACTH	+	5.321
,, ,,	Aldosterone, salt retention	adenohypophysis, ACTH	?	5.311

* The hormones secreted by these glands also have important morphogenetic actions.

† + = stimulation of secretion
— = inhibition of secretion
? = control uncertain

and a low level the glucagon, in such species as have this hormone (Saka, 1952). Between them, the two hormones keep the sugar level relatively constant; but their action is rather synergistic than antagonistic, as the terms diabetogenic and antidiabetogenic suggest. Glucagon mobilizes glucose from store and releases it into the blood; the resulting increase stimulates the secretion of insulin which lowers the sugar level in the blood, by facilitating its passage into the tissues where it can be utilized. This lowering in blood-sugar level again stimulates glucagon secretion and the see-saw continues.

This seems to be the only form of control that there is over the secretion of insulin. The case of glucagon is different, in that its secretion can also be stimulated by the endocrinokinetic hormone, STH (§§4.222 and 5.523). This has led to the erroneous impression that insulin secretion is also stimulated by STH; but it seems that the action is indirect, through the effect of glucagon on the level of sugar in the blood. The action of STH in stimulating growth is due to its increasing the secretion of glucagon, and thereby enlisting the synergic action of insulin to provide the tissues with more glucose. If the supply of insulin falls short, further injection of STH fails to induce any further growth (Owen and Engel, 1957).

The only other case of direct control of a metabolic hormone is that of the parathyroid glands, which are stimulated to secrete parathormone by a high concentration of phosphates or a low level of calcium in the blood. The parathormone then reduces the phosphate and raises the Ca levels until they pass beyond the threshold values for stimulation of the hormone (§ 5.422). If low calcium and high phosphates are maintained in the blood of mammals for some time, they cause hypertrophy of the parathyroid glands.

As in the case of insulin, earlier reports suggest that the parathyroid glands of mammals are stimulated by an endocrinokinetic hormone, either thyroxine from the thyroid or TSH from the hypophysis. The actions of these hormones are now interpreted as indirect effects, mediated by the increase in blood phosphates which they induce. In fish, the homologous ultimobranchial body of *Astyanax* has been shown to hypertrophy, in a similar way to the parathyroid, in response to stimuli leading to a rise of phosphates in the blood. Yet the administration of thyrotrophin, TSH (§ 4.221), which might be expected to increase phosphates through its action on the thyroids (§ 5.421), was followed in *Xiphophorus* by the almost complete destruction of the ultimobranchial body (Rasquin and Rosenbloom, 1954). The indirect relation of the ultimobranchial body to activity of the hypophysis also differs apparently in the eel, *Anguilla*, from that in *Astyanax* and *Fundulus* (§ 5.411). The situation in the Amphibia also remains obscure.

It may be noted that the three metabolic hormones which can be controlled directly and be kept in balance by the effects of their own action are all secreted by endodermal endocrine glands. The kinetic hormones controlled in a similar way are all secreted from isolated cells, but they also come from the gut, which is endodermal. It is, therefore, interesting that the secretion of the thyroid gland, with its predominantly morphogenetic actions, is not controlled in this way, although it is formed from gut cells.

5.522 *Nervous control of secretory cells of nervous origin*

The metabolic hormones secreted from neurosecretory cells are controlled by nerves in all cases that have been sufficiently fully investigated. Among the Crustacea, the best established case is that of the diabetogenic hormone from the sinus gland, the secretion of which is impeded by sectioning its nerve supply from the brain (§ 5.211). In the case of the moult-inhibiting hormone, associated with the restraint of protein catabolism and the increase of water diuresis, it is possible (though as yet unproven) that the nervous action is one of inhibition, which allows moulting to occur. The implantation of isolated sinus glands can have at least some of the normal effects of the glands *in situ*, as though nerve stimulation is not necessary to induce secretion. The effect of nerve section, rather than gland removal, in inducing forced moults and the accompanying metabolic changes, has not apparently been investigated.

Among Insecta, the brain can only inhibit the secretion of the diapause hormone from the suboesophageal ganglia if the nerves connecting them are intact (§ 5.112). In Vertebrata, the secretion of ADH from the neurohypophysis responds to nervous stimuli initiated from osmoreceptors in the hypothalamus, where they receive capillaries from the carotid arteries (§ 5.322). The nervous control of the secretion of oxytocin, which is believed to stimulate the excretion of salt, has not been established (§ 5.312); but it might be expected from the fact that the secretion of oxytocin, when it causes milk "let-down", is clearly under nervous control and can be inhibited by anaesthesia (§ 3.114, Fig. 3-8).

This suggests that the release of the active chemical from a neurosecretory cell is usually under nervous control; but it is not clear whether its own axon serves to transmit nerve impulses to the distal point where secretion is released or whether some other release mechanism is stimulated by impulses from the adjacent neurones with which it remains in contact.

5.523 *Hormonal control of endocrine glands*

The remaining endocrine glands which secrete metabolic hormones are all under some form of control by endocrinokinetic hormones (§ 4.2).

Among Crustacea, evidence is accumulating for the moult-promoting hormone from the Y-organ being stimulated by an endocrinokinetic hormone released from Hanström's sensory pore organ (§ 4.211). There is well-established evidence in Insecta for ecdysone, the morphogenetic moult-promoting hormone from the prothoracic glands, being controlled by a neurosecretion from the brain, acting as an endocrinokinetic hormone (§ 4.212). The same prothoracotrophin may be expected to stimulate the release of the antidiabetogenic hormone and the hormone which decreases blood phosphates, which are released simultaneously with ecdysone from the same glands, and are assumed to be identical with it. Neither their identity nor the means of stimulating their secretion has so far been established specifically.

Control of the corpora allata of insects is less well understood than that of the prothoracic glands. The formation and release of their secretion is subject to inhibition by nerves from the brain; their growth can be stimulated by a neurosecretion from the brain (§ 4.213), passed to them via the store in the corpora cardiaca (rather as the growth of the thyroid gland can be stimulated by TSH); there are also indications that secretion of the hormone or hormones from the corpora allata may be increased, if not solely stimulated, by the same neurosecretion from the brain, but the evidence does not seem to be conclusive (Thomsen, 1952).

The endocrinokinetic hormones stimulating the formation and release of metabolic hormones from endocrine glands in vertebrates are well known and are all derived from the adenohypophysis. Adrenocorticotrophin, ACTH, stimulates the secretion of at least one of the metabolic hormones from the adrenal cortex (§ 4.231). These have no morphogenetic actions; but glucagon and thyroxine have these, in addition to their effects upon metabolism. The growth-promoting action of glucagon, stimulated by STH, has already been mentioned (§ 4.222). Thyroxine, the secretion of which is stimulated by TSH (§ 4.221), has the most specific morphogenetic actions, such as the control of amphibian metamorphosis.

5.53 HORMONES AND THE ENVIRONMENT

Many of the relatively quick-acting kinetic hormones induce protective responses to the environment, and maintain short-term changes in diurnal and tidal rhythms. Their release is often directly controlled by the nervous system, and serves mainly to relieve the latter of some of its rather slower and less specific functions. The metabolic hormones control the "internal milieu" in the tissues: while some tend to maintain a steady balance, others allow of relatively slow adaptation to environmental changes. Most of these hormone-controlled responses are initiated by the nervous system, some directly, and others only indirectly through the mediation of a second, or endocrinokinetic, hormone. This last type of control of bodily change is well suited to maintaining a particular response over a long period of time. It is appropriate to some metabolic processes such as diapause; but it seems best fitted to relate the secretion of morphogenetic hormones concerned with growth and reproduction to seasonal changes in the environment. This complex field of hormonal activity must, however, be left to the second part of the book.

5.6 References

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GLOSSARY

(Hormones are marked with an asterisk)

A.C.E.: Extract of adrenal cortex of vertebrates.
*ACH: Hormones of adrenal cortex of vertebrates.
*ACTH: Adrenocorticotrophic hormone from vertebrate adenohypophysis.
*ADH: Antidiuretic hormone from vertebrate neurohypophysis.
Adrenalectomy: Operative removal of the adrenal body and especially of the adrenal cortex.
Allatectomy: Operative removal of the corpus allatum.
Antidiuretin: A commercial product containing *ADH.
Antuitrin: A commercial extract of the anterior lobe of mammalian pituitary body (i.e. of the adenohypophysis).
ATP: Adenosine triphosphate, a phosphagen with a high-energy phosphate bond.
*B: Intermedin or melanophore-dispersing hormone (*MSH) from pars intermedia of vertebrates.
C: Carbon.
C^{14}: Radioactive isotope of carbon.
Ca: Calcium.
*CBLH: *Crago*-body-lightening hormone, concentrating black pigment in melanophores on body of shrimp; present in brain extracts.
C_{CR}: Rate of creatinine clearance in urine.
*CDH: *Crago*-darkening hormone, dispersing black pigment in all melanophores of shrimp; present in commissure extracts.
C_{H_2O}: Rate of clearance of "free" water.
Cl^-: Chloride ion (anion).
cm^3: Cubic centimetre or millilitre.
C.N.S.: Central nervous system.
CO_2: Carbon dioxide.
CRF: Cortical-releasing-factor, acting on pars distalis of vertebrates.
*CTLH: *Crago*-tail-lightening hormone, concentrating black pigment in melanophores on the tail of shrimp; released from sinus gland.
*CWCH: *Crago*-white-concentrating hormone, concentrating pigment in guanophores of shrimp. Source uncertain.
*CWDH: *Crago*-white-dispersing hormone, dispersing pigment in guanophores of shrimp. Source uncertain.
*D: Diapause hormone, from suboesophageal ganglion of insects.

*EDH: *Eupagurus*-darkening hormone, dispersing red pigment in erythrophores of hermit crab. Source uncertain.

*ELH: *Eupagurus*-lightening hormone, concentrating red pigment in erythrophores of hermit crab. Source may be in eyestalk.

Endocrinokinetic: of hormones stimulating the secretion of other hormones from endocrine glands.

ES: Eyestalk of decapod and stomatopod Crustacea.

*FSH: Follicle-stimulating hormone from adenohypophysis of vertbrates.

GXO: eNeurosecretory cells forming ganglionic-X-organ in the optic ganglion of Crustacea.

g: Gramme.

G.F.R.: Glomerular filtration rate.

H^+: Hydrogen ion.

HCl: Hydrochloric acid.

H_2O: Water.

HSPO: Hanström's sensory pore organ, a storage-and-release organ in Crustacea.

Hypophysectomy: Removal of the hypophysis or pituitary body, including the neural lobe unless otherwise stated.

I: Iodine.

I^{131}: Radioactive isotope of iodine.

*ICSH: Interstitial-cell-stimulating hormone from adenohypophysis of vertebrates.

*J (or JH): Sometimes used for juvenile hormone inhibiting metamorphosis of insects; secreted from corpus allatum.

K^+: Potassium ion.

kg: Kilogramme = 1,000 g.

l: Litre.

*LDH: *Ligia*-darkening hormone, dispersing black pigment in melanophores of an isopod. Source unknown.

*LH: Luteinizing hormone from adenohypophysis of vertebrates.

*LLH: *Ligia*-lightening hormone, concentrating black pigment in melanophores of an isopod; probably released from organ equivalent to sinus gland within head capsule.

l.n.c.: Lateral neurosecretory cells in insect brain.

*LSH: Luteal-stimulating hormone from adenohypophysis of vertebrates. Appears to be identical with *prolactin.

*LTH: "Luteotrophin", = LSH.

*MCH: Melanophore-concentrating hormone, concentrating black pigment in fish; secreted by adenohypophysis.

mEQ: Milli-equivalents or equivalent weight in grammes × 10^{-3}.

mg: Milligramme.

micro-EQ: Micro-equivalents or equivalent weight in grammes × 10^{-6}.

*MIH: Moult-inhibiting hormone of Crustacea, released from sinus gland.

ml: Millilitre or cubic centimetre.

mm Hg: A measure of pressure in millimetres of mercury.

m.n.c.: Median neurosecretory cells in insect brain.

Molar: A solution of a substance containing its molecular weight in grammes per litre.

*MPH: Moult-promoting hormone of Arthropoda (=*ecdysone of Insecta). Sources in antennary or maxillary glands.

*MSH: Melanophore-stimulating hormone or *B, dispersing black pigment in cold-blooded vertebrates; secreted from pars intermedia of adenohypophysis.

MTU: Methylthiouracil.

N: Nitrogen. Also used for a "normal" solution of any chemical substance containing its equivalent weight in grammes, dissolved in one litre of water.

Na^+: Sodium ion (cation).

NaCl: Sodium chloride.

$NaHCO_3$: Sodium bicarbonate.

Nephrectomy: Operative removal of the kidneys.

O_2: Oxygen molecule.

P: Phosphorus, the characteristic element in phosphates.

*PDH: *Palaemonetes*-darkening hormone, dispersing red pigment in chromatophores of Crustacea (Decapoda, Natantia). Source uncertain, but can be extracted from C.N.S.

Peristalsis: rhythmic contraction of longitudinal muscles, e.g. for driving the contents along the intestine.

pH: Hydrogen ion concentration (=negative logarithm; e.g. 10^{-7}N ions is given as pH 7.0).

Pitocin: A commercial extract of the posterior lobe of the mammalian pituitary body containing mainly * oxytocin.

Pitressin: A commercial extract of the posterior lobe of the pituitary body, containing chiefly the "pressor" fraction, or *ADH.

Pituitrin: A commercial extract of the posterior lobe of the mammalian pituitary body (i.e. of the neurohypophysis) containing *oxytocin and *ADH.

*PLH: *Palaemonetes*-lightening hormone, concentrating red pigment in chromatophores; released from sinus gland (see PDH).

*PWCH: *Palaemonetes*-white-concentrating hormone, concentrating pigment in guanophores; possibly secreted by the commissures.

*PWDH: *Palaemonetes*-white-dispersing hormone dispersing pigment in guanophores (making animal pale); released from sinus gland.

*RPCH: Retinal-pigment-concentrating hormone of some decapod Crustacea; possibly secreted by the commissures.

*RPDH: Retinal-pigment-dispersing hormone of some decapod Crustacea; released from sinus gland.

SG: Sinus gland of Crustacea, a storage-and-release organ for several hormones from neurosecretory cells in brain and GXO.

s.n.c.: Neurosecretory cells in the suboesophageal ganglion of insects.

Steroids: 17-OH steroids. Characteristic secretions of the adrenal cortex, as in 17-hydroxycorticosterone or hydrocortisone.

*STH: Somatotrophin, or growth hormone, from adenohypophysis of vertebrates, stimulating secretion of *glucagon.

Sudanophilic: of tissues with lipids which dissolve, and become coloured easily by, Sudan reds or black.

*TSH: Thyrotrophin, or thyroid-stimulating hormone, from adenohypophysis of vertebrates.

*UDH: *Uca*-darkening hormone, dispersing black pigment in melanophores of Crustacea, such as crabs (Decapoda reptantia, Brachyura); released from sinus gland.

*ULH: *Uca*-lightening hormone, concentrating black pigment in crab melanophores. Source unknown.

*URCH: *Uca*-red-concentrating hormones, concentrating pigment in crab erythrophores; present in extracts of C.N.S.

*URDH: *Uca*-red-dispersing hormones, dispersing pigment in crab erythrophores; released from sinus gland.

*UWCH: *Uca*-white-concentrating hormone, acting on pigment in crab guanophores. Source unknown.

*UWDH: *Uca*-white-dispersing hormone, acting on pigment in crab guanophores. Source unknown.

*Vasopressin: name for *ADH in mammals.

*W: Melanophore-concentrating hormone, concentrating black pigment of Amphibia; probably secreted by pars tuberalis of adenohypophysis.

X-organ: Used for two organs in crustacean eyestalk: GXO, and also HSPO, for which it was the original name.

Y-organ: Endocrine gland in head of Crustacea, secreting *MPH.

INDEX OF AUTHORS

References to tables are given in *italics* and to figures in **heavy** type.

Abramowitz, A. A., 74, 191
Abramowitz, R. K., 74
Adams, A. E., 139
Adamsons, K., 37
Alexandrowicz, J. S., 29, 59, **60**
Amar, R., 28
Angerer, C. A., 185
Arvy, L., 30, 37, 135, 218, 236
Astwood, E. B., 143, 147
Atz, J. W., 40, 43, 52, 106, 107, 139, 144, 149, 227, 244

Bacq, Z. M., 39, 73, 116
Bargmann, W., face **22** (g)
Barker, S. B., 141
Barrington, E. J. W., 47, 173
Bartter, F. C., 247, 252
Bastian, J. W., 131
Bates, R. W., 140
Bayliss, L. E., 131, **247**
Bayliss, W. M., 122
Beach, F. A., 70
Bennett, M. F., 94
Berliner, R. W., 238
Berthold, A. A., 1
Bidder, A. M., 116
Bliss, D. E., **24**, 25, 179, **181**
Bloom, B., **198**
Bloom, W., face **22**, 43, face **48**, 50
Blumenthal, H. T., 193
Bodenstein, D., 203
Bogdanove, E. M., 141
Boretti, G., 230
Bozler, E., 72
Briggs, F. N., 143, 144, **146**, 147, **148**
Brooks, F. P., 219
Brown, F. A., 80, 85, 86, 88, 89, **89**, **92**, 93ff., 97, 99, **110**fn.
Brown, F. C., 174, **176**
Bruin, G. H. P. de, 77, 80
Buddenbrock, W. von, face **62**, 63, 67
Burden, C. E., 212

Calhoon, T. B., 185
Cameron, M. L., 59, 62, 77
Campenhout, E. van, 45
Cannon, W. B., face **62**
Carlisle, D. B., 4, 7, 20, 25, **26**, 28, 56, 59, **60**, 77, 83, 86, 89, *98*fn., 109, 135, 167, 221, 222, 242, **242**
Carlson, S. P., face **83**
Chaikoff, I. L., 140
Chatfield, P. O., 186
Chester Jones, I., 193, 205, 212, **213**, 215, 216, **216**, *217*, 219, 226, 228, *229*, 235, 237, 240
Collip, J. B., 246, 249
Conway, E. J., 206
Cornfield, J., 140
Cowie, A. T., 131, 161
Crisp, D. J., 77, 80

Dahlgren, U., 2
Davidson, D. G., 238
Dawes, B., 70
Day, M. F., 117
De Lerma, B., face **22**, **32**, 33
De Robertis, E., face **48**, face **140**, face **141**
Dennell, R., 195

Dicker, S. E., 219
Dubois, F. S., 12
Dupont-Raabe, M., 75, 77, 89, 102, 109

Ebling, J., **194**
Echalier, G., 135
Edwards, G. A., 179, **180**
Enami, M., face **22, 27**
Engel, F. L., 256
Engel, S. L., 37
Engelmann, F., 138
Engfeldt, B., 250, 252
Erspamer, V., 230
Etkin, W., 174
Everett, J. W., 162

Fieser, L. F., **194**
Fieser, M., **194**
Fingerman, M., 80, 85, 99
Fisher, P., 116
Fitzpatrick, C., 99
Fitzpatrick, R. J., 65
Folley, S. J., 131, 161
Fontaine, M., 227, 236, 243, 244
Fowler, M. A., 212, **213**
Frost, R., 179, *179*
Fuhrman, F. A., **210**
Fukuda, S., 182, 183

Gabe, M., 21, 30, 135, 236
Gaines, W. L., 66, **68**
Galli-Maïnini, C., 128
Ghiretti, Fr., 39, 73, 116
Giersberg, H., **75,** 76, **76,** 94
Ginsburg, M., **238**
Goffart, M., 70
Goldstein, M. S., 196, **196,** 197, **198**
Gorbman, A., 173
Green, J. D., **36**
Greer, M. A., 141
Grobstein, C., 141
Grossman, M. I., 5, 45, 63, 64, 117, 119, **121, 122, 123,** 124, 125, **125,** 126, 127
Guyselman, J. B., 221

Hamburger, K., 168, 170
Hane, S., 144
Hanström, B., 2, 28, 32, 102
Hara, J., 59
Harker, J. E., 69
Harris, G. W., 1fn., 37, **42,** 160, 162
Harvey, W., 1
Hasegawa, K., 172, 184
Havel, V. J., 191, *192*, 248, *248*
Healey, E. G., 107, **110**fn.
Heller, H., 219, **238,** 239
Hjerquist, S.-O., 250, 252
Hines, M. N., 80
Hinton, H. E., **137,** 182, 184, 185
Hirsch, G. C., 116
Hisaw, F. L., 191
Hoar, W. S., 174
Hogben, L., between **82** and **83,** 84, 85, 103, **104,** 105, **110**fn.
Houssay, B. A., 128, 197
Hsieh, K.-M., 193
Huddlestun, B., **196,** 197
Huxley, J. S., 2, 6

Ivy, A. C., 119, **121, 122**

Jacobs, W., 116
Jenkin, P. M., 7, 218fn.
Jewell, P. A., 239
Jones, B. M., 184
Jørgensen, C. B., 210, **210,** 215, 218

Karlson, P., 131fn.
Keeton, R. W., 122
Kitching, J. A., 206

Klein, S. P., **196,** 197
Kleinholz, L. H., 26, 80, 82, 100, 179, *179*, 189, *192*, 248, *248*
Knowles, F. G. W., 4, 7, 20, **24,** 25, 28, 29, 56, 77, face **82,** 83, 86, 89, **90,** *98*fn., 109. 135, 167, 222
Koch, F. C., 122
Koch, H. J., 209
Koch, H. J. A., 201, **202**
Koller, G., 2
Kopeć, S., 2
Krijgsman, B. J., 116

Landgrebe, F., **110**fn.
Laviolette, P., 128
Leach, W. J., 174
Lees, A. D., 182, 184
Lender, T., 12
Levi, H., 210
Levine, R., 196, **196,** 197, **198**
Levinsky, N. G., **231**
L'Hélias, C., 191, 205, 250, 251
Luckhardt, A. B., 122
Lüscher, M., 138
Lyman, C. P., 186
Lynn, W. G., 175

Mangold, H., 2
Marsland, D. A., 73
Marvin, H. N., 177
Matthews, L. H., 151
Matthews, S. A., 174
Matty, A. J., 174, **175,** 177
Maximow, A. A., face **22,** 43, face **48,** 50
Mendes, M. V., **32,** 40, 61
Mialhe, P., 193
Mialhe-Voloss, C., 44
Miller, R. M., 193, 194
Mudge, G. H., 227
Müller, J., 139, 174, 177
Munson, P. L., 143, 144, **146,** 147, **148**

Nagano, T., 191
Nalbandov, A. N., 128
Needham, A. E., 201, 205
Neiland, K. A., 188, *188*, 200, *200*
Nikitovitch-Winer, M., 162
Noble, R. L., 199, 205
Nuñez, J. A., 222, **223, 224**

Odiorne, J. M., between **82** and **83,** 97
Oliver, G., 1
Osaki, H., 218
Owen, J. A., 256

Papandrea, D. N., 191
Parker, G. H., 79, 86, 105, **106**
Passano, L. M., 28, 222
Pavlov, I. P., 123
Pauly, J. E., face **48,** 52, **53**
Perkins, E. B., 2, 88
Pfeiffer, I. W., 187
Pickford, G. E., 40, 43, 52, 106, 107, 139, 144, 149, 227, 244
Pickford, M., 219
Pitts, R. F., 250
Polin, D., 246
Potter, D. D., 21, 27
Powning, R. F., 117
Prosser, C. L., 122

Rall, J. E., 177, 187
Rasquin, P., 144, 212, 227, 243, 244, 250, 251, 257
Rawson, R. W., 177, 187
Reichart, R., 191, *192*
Richardson, K. C., **66**
Riddle, O., 177, 193, 197
Rinfret, A. P., 144
Ritchie, J. M., 70
Roberts, K. E., 250
Roberts, S., 144
Roberts, T. W., 69
Robertson, C. R., 119, **121,** 122

Robson, J. M., **65**
Romijn, C., 116
Root, R. W., 174
Rosenbloom, L., 144, 212, 243, 244, 250, 251, 257
Rosenblueth, A., 154
Rosenkilde, P., 215

Saka, M. O., 142, 195, 256
Saloum, R., 179, *179*
Salter, W. T., 140
Sandeen, M. I., **92,** 93, 99
Sawyer, W. H., **210,** 211, **211,** 218, **226, 231,** 232, **232,** 233, **234,** 235, **236,** 238, 239
Sayers, G., **145**
Sayers, M. A., **145**
Scatterty, L. E., 105
Schäfer, E. A., 1
Scharrer, B., 2, 21, face **22,** between **22** and **23,** 31, 32, **34,** 35, **42, 62,** 139
Scharrer, E., 2, 21, face **22,** between **22** and **23,** 31, **34,** 35, **42**
Scheer, B. T., 181, 188, *188*, 191, 200, *200*
Scheer, M. A. R., 181, 191
Schmidt-Nielsen, K., 218
Schneider, F., 185
Schwabe, C. W., 181
Scow, R. O., 141
Scudamore, H. H., 89, 168, 178, **178,** 220, **220,** 221, 248
Selye, H., 5
Sereni, E., 73
Shapiro, H. A., 245, *245*, 249
Simpson, S. A., 143, 216
Slome, D., between **82** and **83**, 84, 85, 103, **104,** 105
Slusher, M. A., 144
Smith, C. L., 128
Smith, D. C., 174, **176**
Smith, D. C. W., 215, 218
Smith, G. C., 177
Smith, H. G., face **83,** *100*, **101,** *102*
Smith, R. I., 80
Sonenberg, M., 177, 187
Spemann, H., 2
Starling, E. H., 1, 122
Staszyc, J., 199
Stephenson, E. M., 84
Stetten, D., **198**
Sturkie, P. D., 246
Stutinsky, F., 230
Sumner, F. B., 70
Swift, D. R., 189

Tait, J. F., 143, 216
Taurog, A., 140
Taylor, A., 176
Thomas, I. M., 173
Thomsen, E., face **23,** 138, 168, 170, **171, 172,** 173, 203, 205, 259
Thomson, D. L., 246, 249
Tinkle, D. W., 85
Tong, W., 140
Travis, D. F., 249
Turner, C. D., 62, **120,** 130

Ussing, H. H., **210,** 233

van Dyke, H. B., 37
Verney, E. B., 239

Wachowski, H. E., 175
Waggener, R. A., 105, 244
Wang, C. C., **123,** 125, **125**
Wang, T.-Y., 193
Waring, H., 105, 109, **110**
Wastl, H., 131
Webb, D. A., 222
Webb, H. M., 80, **92,** 93, 94
Weber, H., **30**

WELSH, J. H., 3, **24,** 25, 37, 56, 59, 61, face **68, 78,** 80, **81**
WILLIAMS, C. M., 136, **137,** 182, 184
WINTON, F. R., 131, **247**
WIRZ, H., 238
WITSCHI, E., 151
WOERDEMAN, M. W., 40fn.
WURSTER, D. H., 193, 194

YAPP, W. B., 6
YOUNG, F. G., 142
YOUNG, J. Z., face **22,** 23, **23,** 69

ZARROW, M. X., 131
ZERAHN, K., 210
ZWARENSTEIN, H., 245, *245*, 249

INDEX OF ANIMAL NAMES

Page references are given under Latin names, even though the animal may be referred to in the text by its common name. References to groups of animals are given in the Subject Index. References to tables are given in *italics* and to figures in **heavy** type. The systematic position of each genus is indicated in brackets, following as a rule the relevant classifications given in either Imms, A. D. (1957), *A General Text Book of Entomology*, London: Methuen and Co; or Marine Biological Association (1957), *Plymouth Marine Fauna;* or Young, J. Z. (1950), *The Life of Vertebrates*, Oxford: Clarendon Press.

Acanthias, spiny dogfish (Pleurotremata), **110**
Alligator, alligator (Crocodilia), 237
Amblystoma, axolotl larvae (Urodela), 175, *208*, 218
Ameiurus, catfish (Ostariophysi), *87*, 107, 108, **110**
Amia, bowfin (Holostei), **36,** 52
Ammodytes, sand-eels (Acanthopterygii), 236
amphioxus, see *Branchiostoma*
Anchistioides, Bermudan shrimps (Decapoda natantia, Caridea), 80
angel fish, see *Rhina*
Anguilla, eels (Apodes), *87*, 105, **106,** 107, **110,** 213, 243, 244, 257
Anisotarsus cupripennis, a beetle (Coleoptera), *208*, 222, **223, 224**
Anolis, climbing lizards (Squamata, Iguanidae), 85, 107, **110**
Antheraea pernyi, a moth (Lepidoptera), 184
Arion, slugs (Gastropoda, Pulmonata), 128
ascidian, see *Perophora*
Astacus, European crayfish (Decapoda reptantia, Astacura), 79, 116, 117, 179, *179*, 189, *190*, 191, *192*, *208*, *241*, 242, 248, *248*
Astyanax, Mexican cave fish (Ostariophysi), 144, *241*, 243, 244, 251, 256, 257
axolotl larva, see *Amblystoma*

Bathystoma, Bermudan white grunt (Acanthopterygii, Haemulidae), 174
beetles, see *Anisotarsus*, *Hydrous* and *Tenebrio*
bitch, see *Canis*
Blabera, a cockroach (Dictyoptera), 230
Blaptica, a cockroach (Dictyoptera), *208*, 222
blowfly larvae, see *Calliphora*

Bombyx, Japanese silkworm (Lepidoptera), 136, *169*, 182, 183, 184, 185, 186
bowfin, see *Amia*
Branchiostoma, amphioxus (Cephalochordata), 47, 173
Buccinum, whelks (Gastropoda, Prosobranchia), 116
Bufo, toads (Anura), 128, *129*, 130, 197, *208*, 210, **210,** 233
B. americana, terrestrial toad, 232
B. arenarum, sand toad, 128, 235
B. bufo, common toad, **210,** 232, 235
B. marinus, South American toad, 235
bug, blood sucking, see *Rhodnius*
bullfrog, see *Rana catesbiana*

Callinectes, blue crab (Decapoda reptantia, Brachyura), 21, 27, 189, *190*, 191, *192*, 195
Callionymus, dragonet (Acanthopterygii), 218, 236
Calliphora erythrocephala, blowfly (Diptera), face **23,** *133*, 135, 138, 168, **171,** 172, **172,** *190*, 195, 203, 250
Cambarus, American crayfish (Decapoda reptantia, Astacura), *58*, 69, *71*, **78,** 79, 80, 108, 168, *169*, 178, **178,** 179, *208*, 220, **220,** 221, 248
Camelus, camel (Artiodactyla), 35
Cancer pagurus, edible crab (Decapoda reptantia, Brachyura), 57, *58*, **60,** 80
Canis, dogs (Carnivora), face **22, 34,** 35, 50, *58*, 66, 67, **68,** 119, **121, 122,** 123, **123, 125,** *133*, 142, 147, *190*, 194, **194, 196,** 197, 219, 237, 238, 239, *241*, 246, **247,** 249, 253
Carausius (=*Dixippus*), stick insect, or "walking stick" (Phasmida), *71*, 74, **75, 76,** 77, 85, 88, 102, 108, 153, 158, *169*, 186, *190*, 191, 203, 225, *241*, 250, 251
Carcinus, shore crabs (Decapoda reptantia, Brachyura), *190*, 201, *204*, 205, *208*, 221, 222, 223, 240, *241*, 242, **242**
carp, see *Cyprinus*
Cavia, guinea pig (Rodentia), face **140**
cat, see *Felis*
catfish, see *Ameïurus*
Cervus, deer (Artiodactyla), 151
chameleon, see *Lophosaura*
Chaoborus (=*Corethra*), phantom midge (Diptera), *87*, 102
chick, see *Gallus*
Chironomus, gnat (Diptera), 209
cockerel, see *Gallus*
cockroach, American, see *Periplaneta*
  viviparous, see *Leucophaea*
cockroaches, see *Blabera* and *Blaptica*
Columba, pigeon (Columbiformes), 130, 177, *190*, 193, 197
Corethra, see *Chaoborus*
cormorant, see *Phalacrocorax*
crab, blue, see *Callinectes*
  dromian, see *Dromia*
  edible, see *Cancer*
  fiddler, see *Uca*
  grapsoid, see *Hemigrapsus*
  hermit, see *Eupagurus*
  land, see *Gecarcinus*
  mitten, see *Eriocheir*
  shore, see *Carcinus*
  spider, see *Maia*
crabs, see also Brachyura and *Sesarma*
Crago (American for *Crangon*), 77, *87*, 94, 95, *96*, 97, *98*, 108

Crangon, shrimp (Decapoda natantia, Caridea), 2, 95, 242
crayfish, European, see *Astacus*
  American, see *Cambarus*
cuttlefish, see *Sepia*
Cyprinus, carp (Ostariophysi), 107
Cyprinus carassius (=*Carassius auratus*), goldfish, 139, 174, 177, 215

deer, see *Cervus*
Diplazon fissorius, an Ichneumon (Hymenoptera), 185
Dixippus, see *Carausius*
dog, see *Canis*
dogfish, rough, see *Scyliorhinus*
  spiny, see *Acanthias*
  smooth, see *Mustelus*
dragonet, see *Callionymus*
Dromia, dromian crab (Decapoda reptantia, Brachyura), 79

earthworms, see Lumbricidae
eel, see *Anguilla*
eel, sand, see *Ammodytes*
Eledone, octopus (Cephalopoda, Octopoda), 21, face **22, 23,** 39, *58*, 69, *71*, 73, 116
Equus, horse, stallion and mare (Perissodactyla), *58*, 63, 70, *129*, 131
Eriocheir sinensis, mitten crab (Decapoda reptantia, Brachyura), *190*, 201, 202, **202,** *204*, 209, 210
Esox, pike (Isospondyli), 107
Eupagurus, hermit crab (Decapoda reptantia, Pagurida), 77, *87*, 93, *98*
E. prideauxi, 84

Felis, cat (Carnivora), between **22** and **23,** 50, *58*, face **62,** 63, 67, 131, 142, *190*, 194, 253
ferret, see *Mustela*
fish, bowfin, see *Amia*
  angel or guitar-fish, see *Rhina*
  catfish, see *Ameiurus*
  dogfish, see *Acanthias*, *Mustelus* and *Scyliorhinus*
  dragonet, see *Callionymus*
  cave-fish of Mexico, see *Astyanax*
  eel, see *Anguilla*
  flatfish, see Pleuronectidae
  goldfish, see *Cyprinus*
  guppy, see *Lebistes*
  killifish, see *Fundulus*
  minnow, see *Phoxinus*
  parrot, see *Pseudoscarus*
  pike, see *Esox*
  salmon, see *Salmo salar*
  sand-eel, see *Ammodytes*
  squirrel, see *Holocentrus*
  stickleback, see *Gasterosteus*
  sword or platyfish, see *Xiphophorus*
  trout, see *Salmo trutta*
  white grunt of Bermuda, see *Bathystoma*
frogs, see *Rana* spp.
Fundulus, killifish (Cyprinodontiformes), between **82** and **83,** *87*, 95, 97, 107, 108, **110,** 212, 226, 243, 244, 257

Gallus, chick, cockerel, fowl (Galliformes), 1, 41, 45, *133*, 142, *190*, 193, 194
Gasterosteus, stickleback (Gasterosteiformes), **110**
Gecarcinus, land crabs (Decapoda reptantia, Brachyura), **24,** 25, 180, **181**
gnat, see *Chironomus*
goldfish, see *Cyprinus*
grasshopper, see *Melanoplus*
grunt, Bermudan white, see *Bathystoma*
guppy, see *Lebistes*

Helix, snails (Gastropoda, Pulmonata), 116
Hemidactylus, lizard (Squamata), 107
Hemigrapsus, grapsoid crabs (Decapoda reptantia, Brachyura), 80, *169*, 187, *188*, *190*, 200, *200*, 202, *204*
Holocentrus, squirrel-fish (Beryciformes), *87*, 94
Homarus vulgaris, lobster (Decapoda reptantia, Astacura), 57
Homo, man (Primates), 1, *58*, 131, 143, 144, 194, 218, 253
horse, see *Equus*
Hyalophora (=*Platysamia*), Cecropia silkworm (Lepidoptera), *133*, 135, 136, **137**, 182, 184 ff.
Hydrous piceus, beetle (Coleoptera), face **22, 32**

ichneumon, see *Diplazon*

killifish, see *Fundulus*

Lampetra, lampreys (Agnatha), 49, *87*, 173
Leander (=*Palaemon*), prawns (Decapoda natantia, Caridea), **24**, 29, 77, 80, 83, 86, 97, 109, 135, 178
L. serratus, common prawn, face **82**, 181
Lebistes, guppy (Cyprinodontiformes), **110**
leeches, see Hirudinea
Leucophaea maderae, viviparous cockroach (Dictyoptera), between **22** and **23**, 31, 32, 61, **62**, 138
Ligia, sea slaters (Isopoda), *87*, *98*, 99ff. *100*, **101**, *102*, 105
L. oceanica, face **83**
Limax, slugs (Gastropoda, Pulmonata), 128
lizard, see *Hemidactylus*
  climbing, see *Anolis*
  "horned toad", see *Phrynosoma*
lizards, 175, 193
lobster, see *Homarus*
lobster, American spiny or rock, see *Panulirus*
Locusta, locusts (Orthoptera), 62
Locustana pardalina, migratory locust (Orthoptera), 184
Loligo, squids (Cephalopoda, Decacera), 23, **23, 72,** 116
Lophosaura, chameleons (Squamata, Chamaeleonidae), 83, 94, 107, **110**
Lymantria dispar, gipsy moth (Lepidoptera), 2
Lysmata seticaudata, Mediterranean prawn (Decapoda natantia, Caridea), **26,** 28, *133*, 135

Maia, spider crab (Decapoda reptantia, Brachyura), 79
man, see *Homo*
Melanoplus differentialis, grasshopper (Orthoptera), **32,** 186, *190*
Mexican cave fish, see *Astyanax*
midge, see *Chaoborus*
minnow, see *Phoxinus*
moth, see *Antheraea*
  gipsy, see *Lymantria*
Mus, mouse (Rodentia), 141
Mustela, ferret (Carnivora), 142, 194, 253
Mustelus, smooth dogfish (Pleurotremata), **110**
mysid prawn, see *Praunus*

octopus, see *Eledone* and *Octopus*
Octopus, octopus (Cephalopoda, Octopoda), 39, 73, 116, *208*

Oryctolagus, rabbit (Lagomorpha), **42**, *58*, 64, **65**, 67, face **68,** *190*, *241*, 249
Ovis, sheep (Artiodactyla), 131

Palaemon, prawns, including Japanese freshwater shrimp (Decapoda natantia, Caridea), *190*, 191
P. serratus, see *Leander*
Palaemonetes, American prawn or shrimp (Decapoda natantia, Caridea), 2, 29, *71*, 80, **81,** 82, 85, 86, *87*, 88, 91, **92,** 93, 94, 95, *96*, *98*, 100
Pandalus, prawn (Decapoda natantia, Caridea), 80
Panulirus, American spiny lobster (Decapoda reptantia, Palinura), *190*, 191, *241*, 242, 249
Paratya, freshwater shrimp (Decapoda natantia, Caridea), *58*, 59, *190*, 191
parrot fish, see *Pseudoscarus*
Penaeus, prawn (Decapoda natantia, Caridea), 29, **90,** 109
Periplaneta, American cockroach (Dictyoptera), *58*, 59, 61, 62, 63, 69, 153, *190*, 203
Perophora, ascidian (Ascidiacea), 173
Phalacrocorax, cormorant (Pelicaniformes), 218
Phoxinus, minnow (Ostariophysi), *87*, 94, 107, 108, **110**
Phrynosoma, lizard or "horned toad" (Squamata), 85, 107
pig, see *Sus*
pigeon, see *Columba*
pike, see *Esox*
platyfish, see *Xiphophorus*
Platysamia, see *Hyalophora*
Praunus, mysid prawn (Schizopoda), 80
prawn, American, see *Palaemonetes*
  common, see *Leander*
  mysid, see *Praunus*
  of Mediterranean, see *Lysmata*
prawns, see also *Pandalus* and *Penaeus*
Pseudoscarus, parrot fish (Acanthopterygii), 47, 139, 174, **176**

rabbit, see *Oryctolagus*
Raja, skates (Hypotremata), **110,** 174
Rana, frogs (Anura), **48,** *58*, 63, 85, *87*, **110,** 122, 124, 140, 153, *169*, 185, 186, 193, 197, *208*, 209, 212, **213**, 226, 227, 230, 231, 232, **232,** 233 ff., 237, 239
Rana, tadpole larva, **48,** 140, 175
R. esculenta, edible frog, **210**
R. catesbiana, bull frog, **211, 234,** 235, 244
R. pipiens, American leopard frog, 105, 226, **226, 231, 236**
R. temporaria, common frog, **210,** 226, 235
Rattus, rats (Rodentia), *14*, 37, 52, **53,** *58*, face **62,** 64, 70, *133*, 140, face **141,** 143, 144 ff, **146, 148,** 161, 162, **175, 176,** 177, 187, *190*, 193, 194, **194,** 195, 197, 205, 216, **216,** *217*, 218, 219, 227, 228, *229*, 230, 237, **238,** *241*, 247, 250, 253
Rhina squatina, angel or guitar fish (Pleurotremata), **110**
Rhodnius, blood-sucking bug (Hemiptera), 135

Salamandra, salamander (Urodela), 124, 176
Salmo salar, salmon (Isospondyli), **110,** 124, 144, 213
S. trutta, trout (Isospondyli), 188, 212, 218

Scyliorhinus (=*Scyllium*), rough dogfish (Pleurotremata), *87*, 105, **110,** 173, 174, **175**
Scyllium, see *Scyliorhinus*
Sepia, cuttlefish (Cephalopoda, Decacera), 23, **23,** 116
Sesarma, crab (Decapoda reptantia, Brachyura), face **22, 27**
sheep, see *Ovis*
shrimp, Bermudan, see *Anchistioides*
  common, see *Crangon*
  common American, see *Crago*
  freshwater, see *Palaemon* and *Paratya*
silkworm, Cecropia of America, see *Hyalophora*
  Japanese, see *Bombyx*
skate, see *Raja*
slater, sea, see *Ligia*
slugs, see *Arion* and *Limax*
snail, see *Helix*
snakes, see Ophidia
sow, see *Sus*
sponges, see Porifera
squid, see *Loligo*
squirrel fish, see *Holocentrus*
stallion, see *Equus*
stick insect, see *Carausius*
stickleback, see *Gasterosteus*
Sus, pig, boar and sow (Artiodactyla), *58*, 70
syrphid flies, see Syrphidae

tadpole, see *Rana*, larval
Tenebrio, beetles (Coleoptera), 116
Thunnus germo, tunny (Acanthopgerygii), *190*, 193
toad, African clawed, see *Xenopus*
toad, see *Bufo* spp.
tortoises, see Chelonia
trout, brown, see *Salmo trutta* (=*S. fario* in freshwater)
tunny, see *Thunnus*

Uca, fiddler crabs (Decapoda reptantia, Brachyura), *71*, 80, face **83,** 85, 86, *87*, 88, **89,** 93, 95, *96*, 97 ff, *98*, 108, 179, **180,** 221, 242
urodeles, see Urodela

whales, see Cetacea
whelk, see *Buccinum*

Xenopus laevis, African clawed toad (Anura), between **82** and **83,** 85, *87*, 103 ff., **104, 106, 110,** 131, 232, *241*, 244, 245, *245*, 248
Xiphophorus, platyfish (Cyprinodontiformes), 257

INDEX OF SUBJECTS

References to tables are given in *italics* and to **figures in heavy** type. References to groups of animals appearing in the text are given in this index; but further references in italics to particular animals, e.g. (*and see Canis*) indicate important entries in the Animal Index.

Abdominal ganglia, 29, 91, **92**
Acetylcholine, 2, 21, 56, 109, 122
Activation, mechanical, 4, 5
Activators, 2ff.
  circulatory, 3ff.
Active transport, of ions, 206, 209ff., **214**, 218, 221ff., 227, 252
  of water, not postulated, 221, 235
Activity, level of, 155
  locomotor, 69, 70
  nocturnal, of *Periplaneta*, 69, 153
Adaptation, to dark and light, **75**, 76, 77, **78**, 79, **81**
  terrestrial, 37, 232
Adenohypophysis, **34**, **36**, 38, 40ff., 40fn., **42**, **48**, 105 (*see also* Hypophysis, Pars distalis, Pars intermedia, Pars tuberalis, *and* Pro-adenohypophysis)
Adenohypophysis as source, of adrenocorticotrophin, ACTH, *14*, 15, 143ff., **145**, 146, **146**, 194, 205, 211
  of endocrinokinetic hormones, 10, 132, 160, 162, *255*, 259
  of gonadotrophins, ICSH and LSH, 6, 149ff.
  of growth hormone, STH, 142
  of kinetic hormones, 22, 56, 107
  of morphogenetic hormones, FSH and LH, 128, 148, 150ff., 162
  of prolactin, LSH, 130, 150
  of thyrotrophin, TSH, 139ff., 177
Adenohypophysis, cells in, 43, 44
  control of secretion, 41, *157*
  development of, **48**, 160
  in fish, 40, 107, 212
  structure of, **34**, **36**, 40ff., **42**
  transplantation of, 141, 161ff.
Adenosine triphosphate, *ATP*, **194**, 196
Adrenal cortex, and balance of salts and water, *208*, 210ff., 218, 219, 220, 225ff.
  and Ca, *241*, 249
  and diabetogenic hormone, *190*, 193ff., **194**, 197, 253
  and metabolic hormones, 185ff., 205, *255*
  and P, *241*, 250
  as source of hormones, ACH, *14*, 15, 50ff., *51*
  cells of, face **48** (*c*), 50ff.
  separate control of weight and secretory activity, 143
  stimulated by ACTH, 15, *133*, 143ff., **145**, **146**, **148**, **194**
  structure of, face **48** (*c*), 50ff., *51*, **53**
Adrenal glands, 38, 38fn., 51
Adrenal medulla, 1, 19, 20, *22*, 33, 37ff., 38fn., 50ff.
  cells of, face **22** (*f*), 37
  nervous stimulation of, *156*, 159
  source of kinetic hormone 37, 63, 68 (*see also* Suprarenal gland)
Adrenalectomy, 193, 212, **213**, 216, **216**, 217, 219, 228, 229, 249
Adrenaline, 1, *8*, 37, 59, 61, 68, 70, 122, 152
  and ACTH secretion, 147, **148**, 195

Adrenaline,
  and chromatophores, between **82** and **83**, *87*, 94, 97, 107, 153
  and glands, 122, *129*, 131
  and muscles, *8*, *58*, **60**, 61ff., face **62**, 63, 67ff., face **68**, 70
  at sympathetic nerve endings, 2, 21, 61
  destroyed by an enzyme, 62
  effects of dosage, 59, 67, 153, 154
  in emergency, 63, 67, *190*, 195
  in invertebrates, 6, 61, 191
  source of, 20, *22*, 37, 38
  stimulation of secretion, 67, *156*
Adrenocorticotrophin, ACTH, *8*, 10, 259
  and adrenal cortex, *14*, 15, *133*, 134, 143ff., **145**, **146**, **148** 154, *157*, 161, **194**, *255*
  in Amphibia, 211, 212, *245*
  in Aves, 193ff.
  in Mammalia, 194, **194**, 205, 218, 219, 228
  in Teleostei, 212, 244
  source of, *22*, 44, *44*, 51, 52
Adrenocortical extract, A.C.E.,**146** 185, 210, 212
Adrenocortical hormones, ACH, (*see also* Aldosterone, Corticosterone *and* Hydrocortisone)
  and metabolism, *169*, 186, *190*, 193, 205, *208*, 210, 212, **214**, 225, 228, 240, 244, 252
  source of, face **48** (*c*), 50ff., *51*, **53**
  stimulated by ACTH, *14*, 15, *133*, 134, 143ff., **145**, **146**, 154, *157*, 161, 211, 219, *255*
Agnatha (including Cyclostomes), **36**, 44, *46*, 47, 83, 173
Albedo (*see* Background response)
Albumen gland, 128, *129*
Aldosterone, *133*, 143, *208*, 216, **216**, 218, 219, *255*
Aldosterone-like hormones, *51*, 143
Alimentary tract, 117ff., **120**
Allatectomy, 168ff., 250, 251, 251fn.
  control operations, 170
All-or-none reaction, 154
Alveoli of glands, 65, **66**
Amino acids, **123**, **125**
Amniota, 41 (*see also* Aves, Mammalia *and* Reptilia)
Amphibia, 2, 12 (*see also* Anura *and* Urodela)
  and balance of electrolytes and water, 207, *208*, 209ff., **210**, **211**, **213**, 218, 225ff., **226**, 230ff., **231**, **232**, 233ff., **234**, **236**
  and calcium, *241*, 244, *245*, 248
  and chromatophores, 74, between **82** and **83**, 83, 85, *87*, 102, 103ff., **104**, **106**, 107, 108, 109, **110**
  and glands, 128, *129*, 131, *133*, 139ff.
  and metabolism, *169*, 173, 174ff., 185, *190*, 193, 197
  control of hormone secretion in, 160, 162, 257
  sources of hormones in, 33, **36**, 38, 43, 44, **48**, 49
Anaesthesia, inhibiting milk flow, 66, **68**, 258
Annelida, 2, 11, 19 (*see also* Hirudinea *and* Lumbricidae)
Antagonistic hormones, 84, 207ff., 252 (*and see* Hormones, antagonistic reactions of)
  possible seat of, in Crustacea, 205
Antennae, effect of removal, 179
Antidiabetogenic hormones, *190*, 195ff. (*see also* Insulin)
Antidiuresis, 207, *208*, **214**, 219, 227, 228ff., 233, 237ff., **238**
Antidiuretic hormone, ADH, and tissue permeability, *8*, 67fn., *208*, 230ff., 230fn. (*see also* Vasopressin)

Antidiuretic hormone, ADH, and tissue permeability,
  in Amphibia, 211, 225, **226,** 230ff., 231, **231, 232, 234, 236,** *245*
  in Mammalia, **214, 216,** *217*, 219, 228, 237ff., **238**
  in Reptilia, 237
  in Teleostei, 235ff.
Antidiuretic hormone, possible analogue in Crustacea, 252
  secretion of, 159ff., *254*, 257
  source of, 35ff.
Antidiuretin, 67fn., 230fn., 233ff., 238
Antuitrin, 97, 107, *245*, 246
Anura, 35, **36,** 41, **110,** 128 (*and see Bufo*, *Rana and Xenopus*)
Apterygota (wingless insects), 31
Arteries,
  carotid, 258
  hypophysial, 41, **42**
Arthropoda, 2, 10, 18, 19, 35, 38 (*see also* Crustacea *and* Insecta)
  kinetic hormones of, 57, 86, *87*, 116ff., 134ff.
  metabolic hormones of, 168ff., 189ff., 195, 199ff., 205, 240
Ascorbic acid in adrenal cortex, 145ff., **145, 146, 148**
Asphyxia, causing stress, 189ff., *192*
  and low blood-Ca, 246ff.
Aves (birds),
  kinetic hormones of, *118*, 122, 124, 128, *129*, 130, 140, 142, 149
  metabolic hormones of, *169*, 173, 177, *190*, 193, 197, *208*, 218, 237, *241*, 245, 253
  sources of hormones in, *22*, 33, 44, *46*, 51, *51*
Axon, 258
  of nerve cells, 2, 19, face **22,** 23, 135, 139
Axon of neurosecretory cells, 4, 19, 20ff., face **22,** between **22** and **23, 23, 24, 26,** 29, **32,** 35, 139
  section of, **34,** 35, **62,** 138
Axoplasm current, 20

B, (*and see* Melanophore-stimulating hormone)
Background (albedo) response, 84, **89,** 154
  in Amphibia, 103ff., **106**
  in Crustacea, 86ff., 94ff., *96*, 97ff., *98*, *100*, **101**
  in Elasmobranchii, 105
  in Insecta, **75,** 76, 102
  in Teleostei, 94, 95ff., **106**
Balance, of calcium, 240ff., *241*
  of monovalent electrolytes, 206, *208*, 209ff.
  of phosphates, *241*, 249ff.
  of water, *208*, 219ff.
Betaine, *71*, 73
Bicarbonate, secretion by pancreas, *118*, **120,** 122ff., **123,** 253
  exchange in kidney, **214**
Bile, 124, 187
Bladder, and water conservation, 230, 233, **236**
Blinding, effect on *Ligia*, 100, *100*
Blood-calcium, 240ff., *241*, **242, 247**
Blood, capillaries, face **68**
  circulation of, 1, 3, 6, 147, 154
Blood-phosphates, *241*, 249ff., 251, *254*, *255*, 258
  and corpora allata, 250
  and cortex, 250
  and ecdysone, 251
  and parathyroids, 243, **247,** 251ff.
  and Y-organ, 249, 251
Blood, plasma, *217*, 233
  pressure, 1, *229*, 233

Blood-salts, 206, **214**
  concentration of, *208*, 209ff., 220ff., 240ff., *241*, **242**
  dilution of, *208*, 218ff., 228ff., *241*, **247**, 247ff., 252
Blood-sugars, 67, 130, 142, *190*
  decrease of, 195ff., **196, 198**
  increase of, 189ff.
  in Crustacea, 189ff., *192*
  in Insecta, 191, 195, 251
  in Vertebrata, 191ff., **194**, 195ff., **196, 198**, 253
Blood supply,
  of adrenal cortex, 52, **53**
  of neurohypophysis, 35
  of pituitary, **36**, 41, **42**
  of thyroid glands, 48
Blood transfusion, 13, face **62**, 73
Blood vessels,
  hormonal control of, 67, face **68**, 230
  hormones released into, 20, **34**, 38, 39, 52, 180
Body fluid in Teleostei, 235
Bone, calcium in, 240, 247
  phosphates in, 249, 252
Brachyura, 25, 80, *87*, 93, 94, 95, *98* (*and see* "crab" in Animal Index)
Brain, action in diapause, **137**, 183
Brain as source of kinetic hormones,
  in Crustacea, 22, **24**, 25, 59, *69*, 87, 98
  in Insecta, *8*, **30**, 31, 61, **62**, 63, 75, *156*
  in Octopoda, 73
  in Vertebrata, 33ff., 64, **106**
Brain as source of metabolic hormones, in Crustacea, 168, *169*, 178, 191, *254*
  in Insecta, *190*, 203ff., *208*, 222ff., **223, 224**, *254*
Brain as source of prothoracotrophin, *22*, 136, **137**, 184, 258
Brain, development of, **48**
  neurosecretion from, 61, **62**, 63, 139
  neurosecretory cells of, face **23, 24**, 25, 26, **30**, 31, **62**, 136, 138, 188, 203, **223**
  sectioning nerves from, 61, **62**, 183, 257
Brain-extract, 25
  in Crustacea, 168, 186
  in Insecta, 102, 223, **224**
Brain hormones (*see* Brain as source of hormones)
Brain structure,
  in Crustacea, 23ff., **24, 26**
  in Insecta, face **23**, 29ff., **30**
  in Vertebrata, 33ff., **34, 36, 48**
Breeding season, 149ff., 259
Brownian movement, 74
Brunner's glands, 126, 127

Calcareous kidney stones, 243
Calcium, balance of, 240ff., *241*
  decrease in blood, 247ff.
  increase in blood, 240ff., *245*
  in Crustacea, 135, 240ff., **242**, 247ff., *248*
  in Insecta, 243
  in Vertebrata, 130, 142, 243ff., **247**, 248
  ions, Ca^{++} (*see* Ions)
  seasonal variations in, 244
Calcium-decreasing hormone, 248
Carausius-darkening hormone, 75ff, **76**, 108, 153
Carausius-lightening hormone, 77
Carbon-dioxide, as parahormone, 2
Carbohydrate metabolism, *8*, 144, 189ff., *190*, 205 (*and see* Blood-sugars)
Carnivora (carnivores), 194, **194** (*and see Canis and Felis*)
Carrier, for hormone, 21, 28, 35
  for ions, 206
Cell membrane, 196, 206

Cell-size, 19, **32**, 39, face **140**, 141
Cells, argentaffine, 45
  chromaffin, face **22** (*f*), 37ff.
  collar, 167
  epidermal, with pigment, 74, **75**
  interrenal, 51
  myoepithelial, 65, **66**, **68**, 153
  of nervous origin, 18ff., 21, *22*, face **22**, 29, **30**, **32**, 33, 45, *156*, 158ff., 257
  of pituitary, 43, *44*
  retinal, 74, 77ff., **78**, **81**, 108
  secretory (*see* Endocrine *and* Exocrine secretory cells)
  sense, **26**
  suprarenal, 51
Central nervous system (*see* Nervous system)
Cephalochordata (amphioxus), 173
Cephalopoda, 18, 21ff., *22*, 23, **23**, 38ff., *71*, **72** (*see also* Octopoda)
  hormones in, 67, 69, 72ff., *156*, 230
Cetacea (whales), 211
Chelonia (tortoises, etc.), 124
Chemical activators, 2ff.
Chemodifferentiation, 3, 4
Chitin, 188, 191, 200, *200*
Chloride ions, Cl^- (*see* Ions)
Cholecystokinin, *46*, 63ff., *58*, **120**, 127, 153, *156*
Cholesterol, 187
Cholinergic nerves, 56, **106**
Chordata, 173 (*see also* Vertebrata)
Chromactivating hormones (chromatophorotrophins), 9, 115
  actions of, 71, 74ff., 82ff., 87
  in Crustacea, 77ff., **78**, face **83**, 86ff., **89**, **90**, **92**, 94ff., *96*, 97ff., *98*, **101**, 108ff.
  in Insecta, 75ff., **76**, 102, 108
  in Vertebrata, 94, 95ff., 103ff., **104**, **106**, **110**
  sources of, **26**, 28, 30, **30**, 59, **106**
Chromatography, paper, 59
Chromatophore, or melanophore, index, between **82** and **83**, 84, 88, **89**, **90**, **92**, *100*, **101**, *102*, **104**
Chromatophores, 9, 72, 79, face **82**, 82ff., *87*
  background responses of, 84, 88, **89**, 91ff., **92**, *96*, *98*, *100*, **106**, 154, 158
  black pigment in (melanophores), between **82** and **83**, face **83**, 83, 85, *87*, 97ff., *98*, *100*, **101**, *102*, **104**, **106**, **110**
  blue pigment in (lipophores), 83
  direct effect of light on, 84, 93, 95, *96*, *98*
  effect of high pressure on, 74
  mixed control of, **106**, 107, **110**
  mixed pigments in, 74, face **82**, 83, 108ff.
  multiple hormone control of, 107ff., 109
  nerve control of, 83, 94, 97, **106**, 107, 109, **110**
  rate of reaction of, 74, 90, **90**, 91, 103, 105, 109
  reactions of, 84ff.
  red pigments in (erythrophores), 77, face **82**, 82, 83, 86ff., *87*, **89**, **90**, **92**, *98*
  reflecting material in (iridosomes), between **82** and **83**, 83
  rhythmic changes in, 85, 86, 93, 99, 103
  white pigment in (guanophores), 77, between **82** and **83**, 83, 85, *87*, 94ff., 96
  with movable pigment granules, 73, 74, face **82**, 82ff., between **82** and **83**, *87*, 107, **110**, *156*, 158
  with muscles, 39, 69, *71*, **72**, 72ff.
  yellow pigment in (xanthophores), between **82** and **83**, 83, 84

- Chromatophores and other pigment cells under hormonal control, *71*, 82ff., 87, 107ff., **110**, *156*, *157*
  - in Agnatha, 83
  - in Amphibia, 83, 103, **104**, **110**
  - in Cephalopoda, 39, **72**, 72ff.
  - in Crustacea, 77ff., **78**, **81**, face **82**, 83, 86ff., *87*, **89**, **90**, **92**, 94ff., *96*, 97, *98*, *100*, **101**, *102*
  - in Elasmobranchii, 83, 105, **110**
  - in Hirudinea, 83
  - in Insecta, 74ff., 102
  - in Pleuronectidae, 83, **110**
  - in Reptilia, 83, 94, 107, **110**
  - in Teleostei, 83, 94, 95, **106**, 106ff., **110**
- Chromatophorotrophic hormones, 9, 82 (*see also* Chromactivating hormones)
- Circumoesophageal connectives,
  - in Crustacea, **24**, 25, 29, **89**, 91, 93, 94
  - in Insecta, 29, **30**, 75, 183, **224**, 225
- Clearance,
  - of creatinine, C_{CR}, **234**, 235
  - of "free water", C_{H_2O}, 214, 227, **234**, 235
- Coloration, protective, 70, 84
- Colour change, 2, 70ff.
  - adaptive, 105 (*see* Background response)
  - diurnal, 85, 86, 93, 97ff.
  - morphological, 70, 84, 160
  - pattern of, 97, 107
  - protective, 9, 95
  - physiological, 70ff., 103, 160
  - rhythm of, 85 (*see also* Rhythm)
- Commissures, *22*, **24**, 25, 28ff., *71*, *87*, 94, *96*, 97, *98*
  - tritocerebral, **24**, 28, 80, **90**, 91, **92**, 94 (*see also* Post-commisure organ)
- Concentrating mechanism in kidney, **214**, 227, 237ff.
- Corpora lutea, 130, 150, 153
- Corpora pedunculata, **30**
- Corpus allatum, 255
  - and fat metabolism, *169*, 186ff.
  - and O_2 *8*, 168ff., *169*, **171**, **172**
  - and P, *241*, 250
  - and protein metabolism, 190, 203ff., *255*
  - and sugar, *8*, 173, *190*, 191
  - cells of, **32**, 39
  - control of secretion and growth of, *133*, 138ff., *254*, *255*, 258
  - morphogenetic actions of, *8*, 12, 39, 170, 250, 251fn.
  - structure of, *22*, **30**, **32**, 33, 38, 39ff., 56, **62**
- Corpus cardiacum,
  - as storage-and-release organ, *22*, **30**, 31ff., 39, 61, **62**, 139, 173, 203ff., 222, 258
  - as source of an intrinsic secretion, 19, *22*, 29, **32**, 33, *58*, 61ff., *156*
  - cells of, 31, **32**, 33
  - extracts of, 61, 77
  - metabolic actions of neurosecretion from, *190*, 203ff., *208*, 222
- Corpuscles of Stannius, 51, *51*, *208*, 227
- Cortical hormones (*see* Adrenocortical hormones)
- Cortical-releasing-factor, *CRF*, 3, 41, 142, 162
- Cortical steroid, 185
- Corticosterone, 216
- Cortisone-like hormone, 250
- *Crago*, chromactivating hormones,
  - and black pigment, CBLH, CDH and CTLH, *87*, 97, *98*, 99
  - and white pigment, CWCH and CWDH, 95, *96*
- Cretinism, 1

- Crustacea, 2, 11, 12, 252ff., *254*, 257, 258 (*see also* Brachyura, Decapoda, Isopoda, Malacostraca *and* Stomatopoda)
  - and control of hormones, 132, *133*, *156*, 159, 254
  - and glands, 116ff., 134ff.
  - and metabolism, 168, **178,** 178ff., *179*, **180, 181,** 186, 187ff., *188*, 189, *192*, 199ff., *200*, **202,** *204*, 205, *208*, 220ff., **220,** 230, 240ff., *241*, **242,** 247ff., 249, 251
  - and muscles, 57ff., **60,** 69, 153
  - and pigmentary effectors, 74, 77ff., **78, 81,** face **82,** face **83,** 83ff., 85, 86ff., *87*, **89, 90, 92,** 94ff., *96*, 97ff., *98*, *100*, **101,** *102*, 108ff.
  - sources of hormones in, 18, *22*, 23ff., **24, 26, 27**
- Cuticle formation, 117
- Cuticle-secreting glands, 117, *129*
- Cyclostomes, **36** (*see also* Agnatha)
- Cystic duct, 63
- Cytochrome *c* system, 182

- Dark-adapting hormones (see Retinal)
- Death,
  - from adrenalectomy, *14*, 15, 216
  - from hypophysectomy, *14*, 64ff.
  - from low blood-Ca, 245
  - from muscular tetany, following parathroidectomy, 244, 246
  - from post-operative shock, *14*
  - from stress, 145
- Decapoda (Crustacea), **24,** 25, **26,** 29, 88, 94ff., *96*, *98*, 108ff., *169*
- Definitions of hormones, 5ff.
- Dehydrating conditions, 233, 236
- Dehydration, of tissues, 207, 228ff., 231, **231,** 233
  - and urine flow in Mammalia, 239
- Desiccation, 37
- Deuterocerebrum, **24,** 25, **30**
- Diabetes, insipidus, *217*, 228, *229*
  - mellitus, 1, 143, 195
- Diabetogenic hormones, 189ff., *190* (*and see* Adrenal cortex *and* Glucagon)
  - endocrinokinetic control of, 142, 144ff., *255*
  - in Crustacea, 189ff., *192*, 257
  - in Insecta, 173, 191
  - in Vertebrata, 144, 191ff., 253ff., *255*
  - nervous control of, 191, 195, *254*
  - sources of, *46*, 50, *51*, 52, 189ff., *190*, 197, 253
- Diapause, 182ff., 259
  - effect of ecdysone on, 136, **137,** 184
  - linked in host and parasite, 185ff.
- Diapause hormone, D, 31, 136, 182ff., *254*, 257
- Digestive, enzymes, 44, 115, 116, 124ff., **125,** 127
  - glands, 117ff., *118*
  - system (*see* Gut)
- Diiodotyrosine, face **48,** 49, 141
- Dipnoi (lung fish), 50
- Diptera (flies), 135ff., 168ff., *169* (*and se Calliphora*)
- Diuresis, phosphate, 251
  - water, 143, 201, 207, *208*, **214,** 219ff., **224,** 225ff., *229*, 235, 240, 257
- Diuretic, extracts of cortex, 226
  - hormone, 201, **216,** 220ff., 222, 223, 225ff., 254, 255 (*see also* Hydrocortisone *and* Sinus gland hormone)
- Diurnal changes in activity of *Periplaneta*, 69, 153
- Diurnal rhythm,
  - in adrenal cortex, 144
  - in calcium metabolism, 242
  - in chromatophores, 85, 86, 103

Diurnal rhythm,
  in epidermal cells, 76
  in hormone secretion, 243, 259
  in retinal cells, 80
Duocrinin, *46*, *118*, **120**, 126, 127, *156*
Duodenum, *46*, 63, **120**, 121, 124, **125**, 126, 127, *156*
Duodenal glands, *118*
Duodenal mucosa, 63, 124, 125, 126

Ecdysone (*see* Moult-promoting hormone of Insecta)
Ectoderm (*see* Endocrine glands from)
Ectohormones, 3
Eggs, growth of, 138
Eggshell and Ca, 246
Elasmobranchii (dogfish and skates),
  and chromatophores, 83, 105ff., 108, 109, **110**
  and control of glands, 122, 124, 139
  and metabolism, 174, 197
  and muscles, 68
  sources of hormones in, **36**, 47, 50ff., *51*
Electrolyte balance, *8*, 10, 143, 206 (*see also* Ions *and* Salts)
  Ca and phosphates, 240ff., *241*, **242**, *245*, **247**, *248*, *254*, *255*
  monovalent, *208*, 209ff., **211**, **213**, **214**, **216**, *217*, 218ff., 240
Electron, micrographs, between **22** and **23**
  microscope, 20
Electrophoresis, paper, 89, 109
Embryos, 2, 3, 4, 35, **48**, 64, 151, 182, 184
Emergency reactions, 63, 67, *190*
Endocrine glands or organs secreting kinetic and metabolic hormones, 8, 61, 184
  cells of, face **22**, **32**, face **48**, **53**, face **140**, face **141**
  direct control of, 253ff., *254*, 257
  ectodermal, 9, 18ff., *22*, **30**, 38ff., 40, **48**, 56, 132, *133*, 134ff.
  endocrinokinetic control of, *14*, 15, 31, 115, 131ff., *133*, face **140**, face **141**, **145**, **146**, **148**, 258
  endodermal, 18, *46*, 46ff., face **48**, 56, 132, *133*, 139ff.
  location of, 119
  mesodermal, 9, face **48**, 50ff., *51*, **53**, *133*, 143ff.
  (*and see 22*, *46*, *51* for names, under which further references to particular glands are given)
Endocrine glands secreting morphogenetic hormones, *8*
  antennary, 12, 134ff.
  gonadial, 70, 128, *133*, 148ff.
  maxillary, 12, 134ff.
  (*and see* Peritracheal, Prothoracic, Thymus, Vas deferens *and* Ventral glands, *and* Y-organ)
Endocrine secretory cells, face **22**, *22*, face **48** (*and see* Neurosecretory cells, *and* cells of Adenohypophysis, Adrenal cortex, Adrenal medulla, Corpus allatum, Corpus cardiacum, Gut mucosa, Islets of Langerhans, *and of* Parathyroid, Salivary, *and* Thyroid glands)
Endocrinokinetic hormones, 7, 9ff., 11, 12, *14*, 15, 115, 131ff., *133*
  actions in Arthropoda, 134ff., 158ff.
  actions in Vertebrata, 139ff., face **140**, 143ff., **145**, **146**, **148**
  and growth, 134, 142, 256
  and kinetic hormones, 128, 149, *157*, 162

Endocrinokinetic hormones,
  and metabolic hormones, 167, *254*, *255*, 258ff.
  and metabolism in Arthropoda, 173, 191, 195, 205, 243, 258 (*see also* Hanström's sensory pore organ *and* Prothoracotrophin)
  and metabolism in Vertebrata, 177, 194, 195, 205, 211ff., 243, 252, 256, 259 (*see also* ACTH, STH *and* TSH)
  and morphogenetic hormones, 12, 134, 148ff., 151ff. (*see also* ICSH and LSH)
  control of secretion of, 145ff., 149ff., 157, 158ff
  sources of, 10, 31, 40, *44*, 160
Endoderm (*see* Endocrine glands from)
Endosmosis, 206, 207, 221, 225, 230
  obligatory, 227, 228, 235
Endostyle, 47, 173, 174
"Energetic hormones", 7
Enterocrinin, *46*, *118*, **120**, 126, 127, *156*
Enterogastrone, *46*, *58*, 64, 117, *118*, **120**, 126, 127, 153, *156*
Environment (habitat),
  adaptation to, 7, 9, 85, 149, 151, 206ff., 240, 259 (*see also* Background)
  and diapause, 182ff.
  aquatic, 225, 228
  arid, 237
  control of, 86
  damp, 222, 230, 232
  dehydrating, 236
  terrestrial, 228, 232
Enzymes,
  and secretagogues, 5, 117
  and thyroxine, 140, 177
  hormone-destroying, 62
  intracellular, 196
  secretion of digestive, 49, 115, 116, *118*, 121, 124ff., **125**, 127
Ephemeroptera (Mayflies), 30, *133*, 135
Epinephrine, **148** (*and see* Adrenaline)
Epiphysis in *Phoxinus*, 94
Epistellar body, 21ff., face **22**, *22*, 23, **23**, *58*, 69, *156*
Epithelium as hormone source, *22*
  coelomic, 38, 50ff., *51*, 52
  ectodermal, 18, *22*, 38
  gut, 46
  stomodaeal, 18, 39, 40, **48**
  thyroid, 48, face **140**, face **141**
Erythrophores (*see* Chromatophores, red pigment in)
Eupagurus, chromactivating hormones, EDH and ELH, 84, *87*, 93, *98*
Excitement, response to, face **62**, 67, 191
Excretion, *208*
  of calcium or phosphates, *241*, 247, 249, 251ff.
  of salts, **213**, **214**, **216**, 218ff., 220, 258
  of sodium ions, *217*, 218, 219, *229*
  of urea, 227
  of urine, **214**, **216**, 227, *229*, 235
  of water, 207, 223 (*see also* Diuresis *and* Water)
Exocrine glands, 9, **66**, 115ff., *118*, *129*
  Brunner's duodenal, 126, 127
  buccal, of Gastropoda, 116
  cuticle-forming, 117, *129*
  digestive, 5, 117ff., 118
  gastric (stomach), 119ff., 126ff.
  in Arthropoda, 116, 117
  nasal, 218
  under hormone control, 44, 45, 115ff., *118*, *129*, 152ff.

Exocrine glands (*and see* Duodenum, Intestine, Mammary, Oviducal, Pancreas, Skin *and* Stomach glands)
Exocrine secretory cells, 49, *118*, 119, *129*, 153
Exoskeleton, 240
Experimental investigations
  examples of, 12ff., *14*, 168ff., 183
  pharmacological methods in, 13, 61, 86, 88, 103, 117ff., 131, 219, **238**
  physiological methods in, 13, face **62,** 85, 103, 119
  use of controls in, 12, 168, **171, 172, 210, 216,** *217*, **226,** *229*, **232, 236, 242,** *245*, 250
Extracts,
  commercial (*see* Antuitrin, Pitocin, Pitressin *and* Pituitrin)
  compared in Crustacea and Insecta, 29
  fractionation of, 89
  of hormone sources (*see* Adrenocortical, Brain, Corpus cardiacum, Eyestalk, Neurohypophysis, Parathyroid glands, Pericardial organs, Sinus gland, Suboesophageal ganglion, Thyroid gland *and* Y-organ)
  relation to hormones, 28, 35, 86, 94, 119
  Upjohn's cortical, 185
  uses of, 13ff., *14*, 51
Eyes,
  adaptation to light, 79, 154
  appositional, 77
  compound, 74, 77ff., **78,** 81
  illumination of, face **83,** 100ff., **101,** 105, **106,** 149
  retinal cells of, *71*
  sessile, 100
  stalked (*see* Eyestalk)
  superpositional, 77
Eyestalk,
  as source of kinetic hormones, 2, *58*, *71*, 108 (*and see* Sinus gland)
  as source of metabolic hormones, 178, *190*, 205, 240, 248, *248*
  extracts of, **78,** 79, 88, **180,** 191
  removal of, **178,** 179, **180, 181,** 187ff., 189ff., 200ff., *204* (*see also* Eyestalkless specimens)
  structure of, **24,** 25ff., **26,** 28
Eyestalk hormones, 2 (*and see* Sinus gland *and* HSPO)
  calcium-decreasing, *241*, 247
  diuretic, 201, **202,** 221ff.
  kinetic, 69, *71*, 81, 153
  metabolic, **178, 180,** 188, *190*, 199ff., *204*, *248*
  moult-inhibiting (*see* Moult-inhibiting)
  source of, 25ff.
Eyestalk tip, *22*, *190*, 205, 252
Eyestalkless test specimens,
  and chromatophores, face **82,** face **83,** 88, **89,** 90ff., **90, 92,** *96*, 97ff., *98*
  and metabolism, 168, **178, 180,** 192, **202, 220,** *248*, 249, 251
Eyestumps, cautery of, 168

Fallopian tube, 65
Fat,
  and flow of hormones, 63, 126
  metabolism of, 168, *169*, 186ff., *188*, 200
Fat-preserving hormone, 188
Fat translocation, 186, *255*
Fatty acids, 63
"Feed-back" control, in Vertebrata, 11, 134, 141, 146, 149, 150, 252
Fish,
  and chromatophores, 73, between **82** and **83, 106,** 108

Fish,
  and control of endocrine glands, *133*, 139, 144, 256
  and metabolism, 174, **175, 176,** 193, 197, 212, 226, 243ff., 250
  sources of hormones in, 33, 35, **36,** 37, 38, 40, 41, 43ff., 49, 50
  (*see also* Elasmobranchii, Holostei *and* Teleostei *and* "fish" in Animal Index)
Flagella, 10, 167
Follicle-stimulating hormone, FSH, *8*, 10
  actions of, *133*, 150ff., 161
  source of, *44*
"Free water" in kidney tubules, **214,** 225, 227, 235
Fresh water, transfer to and from, 206, 207, 212, 226, 244
Frontal ganglion, **30**
Frontal organ of Apterygota, 31
Fructose, **198**

Galactose, 193, **196,** 197, **198**
Gall bladder, *58*, 63, **120,** 127
Gametes, 8, 152
Gamones, 3
Ganglion,
  abdominal, 29, **30,** 91, **92**
  frontal, **30**
  hypocerebral, **30,** 33, 39
  optic, 81 (*see also* Optic lobe *and* Ganglionic-X-organ)
  parasympathetic, 45
  pedal, 23
  stellate, 21, *22*, **23**
  suboesophageal, *q.v.*
  sympathetic, 33, 37, 68
  thoracic, **24,** 29, **30**
  ventral, **24, 30**
  ventricular, **30**
Ganglion cells, **27,** 37
Ganglionic-X-organ,
  as source of hormones, 80, 82, *169*, 178, 179, 188, 191, *208*, *241*, 247ff., 251
  structure of, *22*, between 22 and **23,** 25ff., **24, 26, 27,** 28
Gastrin, 5, 6, *156*
  kinetic actions of, 57, *58*, 64, *118*, 119, 120ff., **120, 121, 122,** 124, 126ff., 152, 153
  source of, 45, *46*
Gastro-intestinal hormones, 45, *46*
Gastroliths, calcareous, in Crustacea, 242
Gastropoda (univalve molluscs), 116, 128, *129*, 163
Genes, 3, 4
Genital (reproductive) ducts, 12, 64ff., 115, 149, 150, 151
Gestation, 152 (*see also* Pregnancy)
Gills, 226, 235
"Glandotrope Wirkung", 131fn. (*see also* Endocrinokinetic action)
Glands (*see* Endocrine and Exocrine Glands)
Glomerular filtrate, 215, 225, 227 228, 233, 238, 251
  reduced volume of, 234
Glomerular filtration rate, G.F.R., 228, *229*, 233, **234,** 235, 237, 239
  unilateral reduction in, 238
Glomerulus, **214,** 233ff., 235
Glucagon,
  control by STH, *133*, 142ff., 193ff., **194,** 199, *255*, 256
  diabetogenic action of, *190*, 193ff., 197, 252, 253, 256
  secretion stimulated by low blood-sugars, 195, *254*, 256
  source of, *46*, face **48,** 50
"Glucagonotrophin", 142fn. (*and see* Growth hormone)
Glucocorticoid hormones, 144 (*and see* Hydrocortisone)

- Gluconeogenesis, 195
- Glucose, 6, 11, 191, 193, **194,** 195ff., **198,** 256
- Glucose-6-phosphate, **194,** 195, 196
- Glycogen, 188, 193, **194,** 195, 196, 200
- Glycoproteins, 43, 173, 174
- Gonads, 4, *8*, 10, 18, 128, *129*, 132, *133*, 148ff., *157*
- Gonadial hormones, 70, 128, *133*, 148ff., 151
- Gonadotrophic hormones, 148ff., *157* (*see also* ICSH and LSH)
- Gonadotrophins, 10, 148, 161
- Graded responses, 154, **238**
- Granules,
  - pigment (*see* Pigment)
  - secretory (*see* Neurosecretory)
- Growth,
  - and Ca and P, 240
  - and metabolism, 253
  - gradients, 3
  - hormone, *8*, 11, 194, 195 (*see also* Somatotrophin)
  - hormone in plants, 3
- Guanophores (*see* Chromatophores, white pigment in)
- Gut,
  - absorptive cells of, 167
  - action of chemicals in, **123,** 124, **125,** 253
  - argentaffine cells of, 45
  - control of digestion in, 115, 117ff., *118*, 127
  - glands of (*see* Endocrine and Exocrine glands)
  - mechanical distention of, 5, 119, **122,** 127
  - mid-, crypts of, 117
  - mucosa, isolated hormone-secreting cells in, 3, 5, 6, 9, 44ff., *46*, 117, 127, 155, *156*, 257
  - muscle (*see* Muscles)
  - water absorption by, 226, 230, 237
- Haemolymph, carrying hormones, 136, **137**
- Haemorrhage, 11, 145, 239
  - non-fatal, 145, **145**
- Hair follicle muscles, 67
- Hanströms sensory pore organ,
  - as source of hormone, *133*, 134ff., 243, *254*, 258
  - structure of, *22*, 24, **26,** 28, 31
- Heart-accelerator hormone, *58*, 59ff., 154, *156* (*see also* Adrenaline)
- Heart beat, *58*, 59, **60,** 62, 67
  - inhibition of, 59
- Heart muscle, 57ff., 63
- Heat,
  - output, 177
  - regulation, 186
- Henle, loop of, **214,** 227
- Hepatopancreas, phosphate content of, 249
- Herring bodies, **32, 34,** 35
- Hexokinase, 196
- Hibernation, 186
- Hirudinea (leeches), 83
- Histamine, 5, 59, 120, 122, 124, 145ff., **145, 146, 148,** *157*
- Histology, 12, 19
- Holocrine secretion, 116
- Holostei (e.g. *Amia*), **36,** 52
- Hormones,
  - actions of, 7, *8*, 56ff., 115ff., 167ff. (*see also* specific effectors and reactions)
  - antagonistic reactions of, 10, 84, 86, 91ff., 103ff., 153, 189, 205, 207, 219, 245, 252, 256 (*and see below*, pairs of hormones)
  - breakdown in tissues, 59, **90,** 91, 140, 155, 184

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Hormones,
  chain reactions of, 9, 11, *14*, 181 (*see also* Endocrinokinetic hormones)
  characteristics of, 6, 152ff., 252ff.
  classification of, 2, 7
  concentration of, in blood, 59, **90,** 99, 109, 141, 145ff., 160 (*and see below*, dosage)
  definitions of, 5ff.
  direct control of, 120, 155, 253ff.
  discovery of, 1
  dosage, effects of, 59, 63, 67, face **68, 92,** 154, **238**
  endocrinokinetic, *q.v.*
  "energetic", 7
  identification of, 12ff.
  in balance with demand, 237
  inhibitory, 6, 126ff., 154, 178ff., 184 (*and see* MIH)
  in host and parasite, 185
  in tissues, 91, 140, 184
  "intracellular", 3
  kinetic, *q.v.*
  metabolic, *q.v.*
  morphogenetic, *q.v.*
  nervous control of, 9, 38, *156*, 158ff., 191, 205, *254*, 257ff.
  pairs of, maintaining balanced reactions, 10, 84, **92,** 107, 153, 189, 207ff., **214,** 219ff., 239ff., 245, 252, 256
  plant, 2, 3
  rate of destruction of, 155
  release of, **23,** 258 (*and see* Storage-and-release organs)
  sources of, 7, 13, *14*, 18ff.
  stimulation of secretion of, 46, 56ff., 131ff., 155ff., *156*, *157*, 253ff., *254*, *255*, 257ff.
  synergistic actions of, 150, 252, 256
  tabulation of, 57 (*and see* List of Tables, p. vii)
  types of, 6ff.
  vascular, 3, 4, 6, *8*, 12, 19 *et seq.*
Hydrochloric acid, and flow of hormones, 123, **123,** 124, **125,** 127, 253
Hydrochloric acid secretion, *118*, 119, **120,** 127, 153
  inhibition by enterogastrone, 126
  stimulation by gastrin, 119, **122,** 127, *156*
Hydrocortisone, and metabolism, *169*, *190*, 194ff., 205, 208, **214,** 216, 225ff.
  stimulated by ACTH, *133*, 228, *255*
Hydrocortisone-like hormones, *51*, 143ff., 205, 225 fn.
Hydrogen ions, H^+ (*see* Ions)
Hydrostatic pressure, affecting vagus, 239
5-Hydroxytryptamine, 116
Hyperglycaemia, 142, 143, 191, 195, 197
Hypertonic, media, 37, 207, 218, 227, 236
  urine, **214,** 239
Hypocerebral ganglion, **30,** 33, 39
Hypoglycaemia, 142, 193
Hypophysectomy, or removal of hypophysis, and ACTH, *14*, 147ff., 212
  and ADH, 67, **231,** 235
  and Ca metabolism, 243, *245*, 246
  and melanophores, 103, **104**
  and oxytocin, 64, 67
  and TSH, 140, 141
Hypophysial, arteries, 41, **42**
  hormones, 142, 152, *245* (*and see* Adenohypophysis *and* Neurohypophysial hormones)
  portal system, 41, **42**
Hypophysis, 40, **48,** 64, 103, **104** (*and see* Adenohypophysis *and* Neurohypophysis)
  and balance of salts, 212ff.

- Hypophysis,
  - and calcium control, 243ff.
  - and phosphate control, 256ff.
  - functions altered by transplantation, 141, 161ff.
- Hypothalamus, and pituitary formation, 40, **48**
  - as source of neurosecretions, 22, 33ff., **34, 42,** 64, 236
  - control of adenohypophysis by, 141, 147, 149
  - injury to, 64ff., 244
  - neurosecretory cells of, 33, 35
  - osmoreceptors in, 235, 239, 257
- Hypotonic, media, 206, 225, 237
  - tissues, 235
  - urine, **214,** 225, 227, 239

- Infundibulum, 35, 40ff., **48**
- Inhibition of reactions,
  - by brain, 183
  - by brain extract, 59
  - by hormones, 6, 58, 64, 126, 153, 178ff., **180,** 184, 200, 203, *204*, 223
  - by nerves, 154, 191, 257
- Inhibition of pigment granule concentration, 74
- Insecta, 2, 11, 257, 258 (*see also* Apterygota, Diptera, Ephemeroptera, Lepidoptera, Odonata, Phasmida, Plecoptera *and* Syrphidae)
  - and control of kinetic hormones, *156*, 160
  - and control of metabolic hormones, *254*, *255*, 257, 258
  - and diapause, 136, **137,** *169*, 182ff.
  - and glands, *129*, 135ff.
  - and metabolism, 186ff., *190*, 191, 195, 203ff., 222ff., **223, 224,** 240, 243, 250, 251
  - and muscles, 56, *58*, 59ff., 62ff., 69
  - and pigmentary effectors, *71*, 74ff., **75, 76,** 82, 85, *87*, 102
  - and respiration, 168ff., *169*, **171, 172**
  - sources of hormones in, 18ff., *22*, between **22** and **23,** face **23,** 29ff., **30, 32,** 38, 39ff., **62**
- Insulin (antidiabetogenic hormone) 1, 6, 8, 15, 253
  - action of, 190, **194,** 195ff., **196,** 197, **198**
  - control of secretion of, 6, 198, 253, 254
  - secretion and STH, 199, 256
  - source of, *46*, face **48,** 49
- Intercerebrum (pars intercerebralis) of Arthropoda, *8*, **62,** *133*, 135ff., 195 (*see also* Neurosecretory cells of)
- Intermedin, 44, *87*, 94, **104,** 107, 160 (*see also* MSH)
- Internal "milieu" in the tissues, 259
- Interrenal body, 38, 50, 51, *51* (*and see* Corpuscles of Stannius)
- Interrenal tissue, anterior, 51, *51*, 144, 212, 226
- Interstitial-cell-stimulating hormone, ICSH, 6, 10, *22*, *44*, *133*, 149ff., *157*
- Intestinal absorption of water, 223, 237
- Intestine (including jejunum and ileum), **120**
  - endocrine secretions of, *46*, 126, *156*
  - exocrine secretions of, 117, *118*, 126
- Invertebrates, 2, 7, 8, 12, 153, 206
  - and glands, 115, *118*, *129*, 132, *133*
  - and metabolism, *169*, *190*, *208*, 228, *241*
  - and muscles, *58*, 61, 64, 67
  - and pigmentary effectors, *71*, 74, *87*

Invertebrates,
  possible hormonal control of salt transport in, 209, 252
  sources of hormones in, 18, 21, 23, 35, 38
Iodides, 140
Iodine, 12, 47, 140ff., 173
  radioactive, 189
Ions (anions and cations),
  active transport of, 206, 209, 215, 218, 221ff., 227, 252
  exchange of, **214,** 216
  Ca^{++}, 221, 240ff., *241*, **242**, *245*, **247,** 248, *254*, 256
  Cl^{-}, 37, 206ff., *208*, 209ff., 212, **214,** 218ff., 221, 252
  H^{+}, **214,** 227
  K^{+}, *208*, 209ff., **214**, 215, **216,** *217*, *229*
  Na^{+}, 206, *208*, 209ff., 212, **213, 214, 216,** *217*, 218ff., 221, *229*, 252
  Phosphate, 240, *241*, **247,** 249, 251, *254*, *255*, 256
Iridosomes, between **82** and **83,** 83
Iris of eye, 67
Islets of Langerhans,
  cells of, face **48** (*b*), 49ff.
  control of, 132, *133*, 142ff., 155, *254*, *255*
  source of glucagon and insulin, *46*, 47, face **48** (*b*), 49ff., 193, 194, 195
Isopoda (*see also Ligia and Paratya*), 28, 29, *98*, 99, **101,** 108

Juvenile hormone, from corpora allata, 12, 39, 251fn.

Kidney tubules, impermeability of, 225, 228
  permeability increased by hormones, **214,** 233ff., 239
  proximal, 225, 227
Kidneys, **214,** 225ff.
  concentrating mechanism in Mammalia, **214,** 227, 237ff.
  creatinine clearance in, **234,** 235
  excretion by, **226,** 235
  reabsorption of water in, 230, 233ff., **234,** 237ff.
  tubular reabsorption of P in, 250, 252
  tubular secretion in, 237
Kinetic hormones, actions of, *8*, 56ff., *58*, *71*, *87*, *96*, *98*, 115ff., *118*, *129*, 259
  and effectors (*see* Chromactivating *and* Endocrinokinetic hormones *and* Exocrine glands *and* Muscles)
  characteristics of, 7, 9, 152ff.
  control of, 155ff., *156*, *157*
  effects of dosage with, 59, 63, 67, 154
  endocrinokinetic control of, 128, 149, *157*, 162
  lack of antagonists for many, 154
  likened to metabolic hormones, 252, 257
  sources of, 18ff., *22*, *46*
Kymograph records, **60,** 62, face **62,** face **68**

Lacertilia (lizards), **36,** 85, 175, 193
Lactation, 152
Lamellibranchia (bivalve molluscs), 115
Larvae in diapause, 184, 185
Lepidoptera (moths and silkworms), 136, 182ff. (*see also Bombyx*, *Antheraea*, *and Hyalophora*)
Light, adaptation to, **75,** 77, **78, 81,** between **82** and **83,** 154
  direct effect of, 77, 84, 85, *96*, *98*
  intensity, 79
  reactions to, 75ff., 83, 84ff., 91ff., **101, 106**

Ligia, chromactivating hormones, LDH and LLH, *87*, *98*, 100ff., **101**

Lipophores, 83

Liver, bile flow from, 124

Locomotion, reduction of, 69, 70

Lumbricidae (earthworms), 4

Lungs, 237

Luteal-stimulating hormone, LSH (*see* Luteotrophin)

Luteinizing hormone, LH, *8*, *44*, 128, 150ff., 152, 161ff.

Luteotrophin, LSH, *22*, *44*, 128, *133*, 150ff., *157* (*see also* Prolactin)

Macrura (= Decapoda, other than Brachyura) *98*fn.

Malacostraca, 26, 28, 82, 83, 93

Malpighian tubules, 63, 223

Mammalia, 1, 253, 256 (*see also* Cetacea, Carnivora *and* Rodentia)
  and balance of electrolytes and water, 207, *208*, **214**, 215ff., **216**, *217*, 219, 227ff., *229*, 230, 233, 237ff., **238**
  and calcium and phosphates, *241*, 246ff., **247**, 249, 250, 251
  and control of endocrine glands, *133*, 140ff., 142, 144ff., **145**, **146**, **148**, 149ff.
  and control of kinetic hormones, 155, *156*, *157*, 160, 162
  and exocrine glands, **66**, **68**, 117ff., *118*, **120**, **121**, **122**, 122ff., **123**, **125**, 128ff., *129*, 130ff.
  and fat, 187
  and intermediary metabolism, *190*, **194**, 194ff., **196**, 197ff., **198**, 205
  and muscles, face **62**, 63ff., **65**, 67, face **68**, 70
  and respiration, *169*, 173, 174, **175**, **176**, 177, 185ff.
  sources of hormones in, face **22**, **34**, 35, 38, 41ff., **42**, 44, *46*, face **48**, 50, 51, **53**, face **140**, face **141**

Mammary glands, 65, **66**, **68**, 119, **121**, *129*, 130, 151ff., 153

Median eminence of vertebrate brain, 35, **36**, 41, **42**, 142

Medium, hypertonic, 37, 207, 236
  hypotonic, 206, 225, 237
  saline, 218, 230ff., **232**
  "outside", 233

Melanin, 75, 76, 83

Melanophore-concentrating hormone, MCH or W, *8*
  in Amphibia, *87*, 103, **104**, 160
  in fish, *87*, 97, 106ff., **106**
  source of (in Pars tuberalis), *22*, 43, 103ff., *157*, 245

Melanophore index (*see* Chromatophore index)

Melanophore-stimulating (dispersing) hormone, B, MSH, or Intermedin, *8*, 102ff.
  in Amphibia, *87*, 103ff., **104**, 160
  in fish, *87*, 94, 97, 105ff., **106**
  in Reptilia, 107
  source of, *22*, 44, 105, *157*

Melanophores (*see* Chromatophores, black pigment in)

Meso- and Meta-adenohypophysis of fish, 40, 107, 212

Mesoderm, as hormone source, 18, 50, *51*
  endocrine cells of, face **48**

Mesodermal endocrine glands, 9, 50ff., *51*, **53**, 143ff.

Mesonephric duct, 52

Metabolic effects, on activity, 69
  affected by endocrinokinetic hormones, 132

Metabolic hormones,
  actions of, 167ff., *169*, *190*, *208*, *241* (*and see* Calcium, Carbohydrates, Electrolytes, Fat, Phosphates, Protein, Respiration *and* Water)
  and internal "milieu", 259
  characteristics of, 7, *8*, 10, 252ff.
  control by feed-back, 11, 134, 252
  control of secretion of, 253ff., *254*, *255*, 259
  endocrinokinetic control of, 132ff., *133*, **137**, 139, 142ff., **145**, 258ff.
  morphogenetic actions of, 173, 257, 259
  pairs of antagonistic, 10, 189, 207ff., **214**, 219, 220, 245, 252, 256
  sources of, 18ff., 38, 40, 44, *46*, 47, 50, *51*, 134ff.
Metamorphosis, *8*, 11ff., 138, 140, 251fn., 259
  in Amphibia, 12, 140, 176
  in Arthropoda, 11, 138
Methylthiouracil, *MTU*, 139
Migration of birds, 149
Milk, 65, **68**, 130
  "let-down", 66, **68**, 152, 154
  pigeon's, 130
Milk-secreting glands, *129*, 130ff. (*and see* Mammary glands)
Mineralocorticoids, 185
Mitosis and secretion, 39, 52, 116, 117
Mitochondria, between **22** and **23**
Moisture,
  and pigmentary effectors, 75ff., **76**, 85
  and water balance, 222, 230, 232
Mollusca, 11, 19, 115ff. (*see also* Cephalopoda, Gastropoda *and* Lamellibranchia)
Monoiodotyrosine, 141
Monosaccharides, 197
Morphogenetic hormones,
  actions of, 128, 134, 139, 148, 149, 150, 151ff. (*see also* Part II.)
  and feed-back, 134
  characteristics of, 4, 7, *8*, 10, 11ff.
  definition of, 7, 11, 167
  distribution of, 11
  endocrinokinetic control of, 10, 132, *133*, 137, 143, 148ff., 162ff.
  kinetic actions of, 70, 128, 149, *157*, 162ff.
  of gonads, *133*, 149ff., *157*, 259
  sources of, 18, 19, 38, 40, 50
Moult-accelerating hormone, from HSPO, 135, *156*, 258
Moult-inhibiting hormone, MIH, of Crustacea,
  and protein metabolism, 200ff., **202**, 203, *204*
  from eyestalk or sinus gland, 12, 135, 186, 187ff., *190*, 221ff., 247, *248*, 252
  nervous control of secretion of, *254*, 257
Moult-promoting hormones, 12, 18
  and diapause, 184ff.
  endocrinokinetic control of secretion of, *133*, *254*, *255*, 258
  of Crustacea, from Y-organ, MPH, 135, *190*, 203, *204*, 222, 240ff., *241*, 251, 252, *254*
  of Insecta, from prothoracic gland, etc. (= ecdysone), *129*, 134, 135ff., **137**, 184, *190*, 195, 241, 251, *255*
  sources of, 18, 38
Moulting, changes in Ca and P during, 240ff., 242, **242**, *248*, 249, 251
  hormonal control of, 8, 11, 117, 134, 135ff., 181, 187, 195, 200, 203, 220, 251fn.

- Moulting,
  - metabolic changes during, 181, 187, 195, 199ff., **202**, 203, *204*
  - water uptake during, 220ff.
- Moults, time of, 40, 74, 200ff.
  - forced, **202**, 221, 257
- Mucosa, 3, 44, 45, 63, 120, 124
- Mucus glands of epidermis, *129*, 131
- Muscle tone, increase of, 69, 70, *156*, *157*
- Muscles, *8*, 9, 13, 56ff., *58*, 152ff., *157*
  - calcium content of, 247
  - of blood vessels, 67, face **68**, 237
  - of chromatophores, 39, *71*, **72**, 72ff.
  - of gall bladder, 63, 127, 153
  - of genital ducts, face **62**, 64ff., **65**, 153
  - of glands, **66**
  - of gut, 57, 62ff., face **62**, 127, 153, 154
  - of hair follicles, 67
  - of heart, 57ff., **60**, 154
  - of iris, 67
  - of mantle, 21, **23**, 69
  - sodium concentration in, *217*, 219
  - somatic, 63, 69ff.
  - specificity of, 153, 154
  - tetany of, 244, **247**
- Myoepithelial cells, *58*, 65, **66**, **68**, 152, 153, 154, 159

- Nasal glands, 218
- Nematocysts, 10
- Nerve,
  - action, 9, 20
  - axons, 19, 41
  - cells, 19ff., face **22**, **32**, 33, 45
  - impulses, 20, 155, 258
- Nerve section, and secretion, 183, 191, *192*, 257
- Nerves,
  - adrenergic, 56, **106**, 131
  - cholinergic, 56, **106**, 131
  - parasympathetic, 45, 62ff., 127, 154
  - stellate, **23**
  - sympathetic, 37ff., 41, **42**, 45, 62ff., 67, 68, 122, 123, 125, 131, 154
  - vagus, 62, 64, 123, 124, 125, 127
- Nervous control,
  - of blood supply, 41
  - of chromatophores, 72, 83, 94, 97, 102, **106**, 107
  - of hormone secretion, 9, **23**, 38, 66, **68**, **101**, **106**, 155, *156*, *157*, 158ff., 191, 205, 219, *254*, *255*, 257ff.
  - of salivary glands, 117
- Nervous system, 7, 155, 205, 259
  - cells derived from, 19ff., face **22**
  - central, of Crustacea, **24**, 24ff.
  - central, of Insecta, 29ff., **30**
  - central, of Vertebrata, 33ff., **48**
  - of Cephalopoda, **23**, 69
  - parasympathetic (*see* Nerves)
  - relieved by hormones, 155
  - stomatogastric, of Insecta, **30**, 39
  - sympathetic (*see* Nerves)
- Neural crest, 45
- Neural lobe of pituitary (*see* Pars nervosa)
- Neurofibrillae, 19
- Nuerohaemal organs, 4, 20, 56 (*and see* Storage-and-release organs)
- Neurohormones, 3, 20, 39, 56, 61, 135, 158
- Neurohumoral secretion, 3
- Neurohypophysial extracts, with frog ADH, 131, **210**, 218, **226**, **232**, **236**
  - mammalian, face **62**, 218

Neurohypophysial hormones, 33, 211, **214,** 219, 230, 233, **234,** 235, 252 (*and see* ADH *and* Oxytocin)
  storage-and-release organs for, *22*, 33, **34,** 35, **42,** 64
Neurohypophysis,
  and kinetic hormones, 64, 67
  and metabolic hormones, *208*, 220, **234,** *241*, 245, 248ff.
  axons in, between **22** and **23** (*g*), **34, 42**
  control of secretion from, *157*, 159ff., 219, 235, *254*, 257
  extract of, face **62** (*and see* Neurohypophysial extracts)
  neurosecretions stored in, **34,** 35, 64, 67, 218, 232, 236
  removal of, *217*, 219, 228, *229*, 231, 235
  structure of, *22*, 33ff., **34, 36,** 40, 41, **42** (= ME + NL), **48**
Neurointermediate lobe of pituitary (*see* Pars intermedia)
Neurons, 2, 19ff., face **22,** 23
Neurosecretion, 4, 10, 19ff., 63
  actions of, 56, 57, 61, 75, 138ff., *156*, *157*, 191, 203ff., *254* (*and see* many Kinetic *and especially* Chromactivating hormones *and* Sinus gland. etc.)
  nervous control of, 10, **23,** *156*, *157*, 158ff., 219, *254*, 257
  sources of, 19ff., **23, 24, 26, 30, 34,** 258 (*and see* Neurosecretory cells)
  storage-and-release of, 20, *22*, 28, **32, 34,** 35, **62,** 203, 236 (*and see* Storage-and-release organs)
Neurosecretory cells, 2, 4, 19ff., face **22**
  compared with neurons, 19ff., 258
  controlled by nerves, *156*, *157*, 158ff., *254*, 257, 258
  in Cephalopoda, 21, **23**
  in Crustacea, 24ff., **24, 26, 27,** 188
  in Insecta, between **22** and **23,** face **23,** 29ff., **30, 32, 62**
  in Vertebrata, 33ff., **34,** 37, 41, **42,** 45, 68
  of intercerebrum (l.n.c. and m.n.c.), *8*, face **23, 30,** 31ff., *133*, 135ff., 173, 195, 203, **223,** 255
  suboesophageal (s.n.c.), 29ff., **30**
  tissue culture of, 35
Neurosecretory, granules, 9, 19ff., face **22,** between **22** and **23** (Figs 2-1 *g* and 2-2), face **23, 27**
  material (Frog ADH), 232
  store, 236
  substances, 9
  systems, *22*, 23ff., **24,** 29ff., 33ff., **34, 62**
Nissl bodies, 19, face **22,** between **22** and **23**
Nitrogen,
  excretion of, 201, *204* (*and see* Protein catabolism)
  metabolism of, 199ff., *200*, **202**
Noradrenaline, 21, 37, 38, 56, 59, **60,** 68
Nutrition, 205

Octopoda (octopus), 21, *58*, 69, 73
Odonata, 135
Oestrogen, *58*, 64, 70, *129*, 130, 131, *133*, 150, 152, *157*
Oestrone, 150 (*see also* Oestrogen)
Oestrus cycle, 70, 131, 150, 151, 152
Ommatidia, 74, 77, **78,** 80, **81,** 100
Ophidia (snakes), **36**

Optic lobe, 24, **24,** 25, 26, **26, 30**
  ganglion in, 26
  terminal medulla of, **24,** 25, **26,** 28
Organiser, 2, 3, 4
Organisine, 3, 4, *8*, 12
Ortho-dihydroxytryptamine, 59
Ortho-diphenol, 61
Osmoreceptors in hypothalamus, 235, 239, 257
Osmotic concentration of urine, 239
Osmotic diuresis, 227
Osmotic gradient, 206, 231, **232,** 233
Osmotic pressure, 74, 221, 227, 235, 237
Ovarian growth, 170
Ovary, 4, 150, 153, *157*, 170, 182, 186
  maturation, 245
Oviducal glands, 128ff., *129*
Ovulation, 246
Oxygen consumption, 167, 168ff., *169* (*and see* Respiration)
  accompanying changes in fat storage, 186, 188
  and TSH, 139
  in Crustacea, 168, 178ff., **178,** *179*, **180, 181**
  in Insecta, 138, 168ff., **171, 172,** 182ff., 191, 250
  in Protochordata, 173
  in Vertebrata, 173ff., **175, 176,** 185ff.
Oxyntic cells, 119
Oxytocin,
  and milk "let-down", 65ff., **66, 68,** 130ff., 154, 159, 258
  and muscles, *58*, face **62,** 64ff., **65,** 67, 152, 153, *157*
  and salt excretion, *208*, 211, **214,** 218, 219, *254*
  and water balance in Amphibia, 230
  source of, 35ff.
Palaemonetes, chromactivating hormones,
  and red pigment, PDH and PLH, *8*, *87*, 91ff., **92,** *98*, *156*
  and white pigment, PWCH and PWDH, *87*, 95, *96*
Pancreas, as endocrine gland, 44, *46*, 132, 142, 193, 194 (*and see* Islets of Langerhans)
  as exocrine gland, 1, 45, 117, *118*, **120,** 122ff., **123,** 124ff., **125**
  transplantation of, 123, **123,** 125, **125**
Pancreatectomy, 193, 197
Pancreozymin, *46*, *118*, **120,** 124, **125,** 125, 127, *156*
Para-activators, 2, 73
Parabiotic graft, 69
Parasympathetic nervous system (*see* Nerves)
Parathormone,
  actions of, *8*, 243, 246, **247,** 250, 251
  means of control, *254*, 256
  secretion of, stimulated by darkness, 246
  source of, *46*, **48,** 49
Parathyroid glands, 49, *241*
  and calcium, *241*, 243, 244, 246
  and phosphates, 250, 251ff.
  cells of, 49
  control by level of Ca and P in blood, 142, *254*, 256
  extirpation of, 246ff., **247**
  extract of, 246, 251
  hypertrophy of, 252, 256
  not under endocrinokinetic control, 132, 142
  secretion stimulated by darkness, 246
  structure of, *46*, 47, **48,** 49
Parathyroidectomy, 246, **247**
Paraventricular nucleus of hypothalamus, *22*, 33, **34,** 35, 37

Pars distalis of pituitary, *22*, **34, 36,** 40, 41, **42,** 43, *44*, *157*, *255* (*see also* Adenohypophysis)
Pars ganglionaris X organi, 25 (*see also* Ganglionic-X-organ)
Pars intermedia of pituitary,
  as source of hormone, 94, 103, **104,** 106, **106,** 107, *157*
  structure of, *22*, **34, 36,** 40, 41, **42,** 43
Pars nervosa (neural lobe of pituitary), **34,** 35ff., **36,** 37, 40fn., **42,** 43, **48** (*see also* Neurohypophysis)
Pars tuberalis of pituitary,
  as source of hormones, *87*, 103, 104, **104,** 105, **106,** *157*, *241*, 245
  regeneration of, 245
  structure of, *22*, **34, 36,** 40, 41, **42,** 43
Parturition, 64, 65, **65,** 152
Pepsin secretion, 119, 120
Peptones, **123,** 125, **125,** 126, *156*
Periodic-acid Schiff reaction, *44*
Pericardial organs, *22*, 25, 29, 57, *58*, 59, *156*
  extracts of, 59, **60**
Perirenal organ, 50
Peristalsis, *58*, face **62,** 62, 63, 155
Peritracheal glands, 135ff.
Permeability of cell membranes,
  decrease in, *208*, 219, 220ff.
  increase in, *208*, 228ff. (*and see* Pores, ultramicroscopic)
  of chromatophores, 74
  of kidney tubules, **214,** 233ff., **234,** 235ff., **238**
  of skin, **226,** 230, **231, 232**
Pharynx, glands of, 44, 46, *46*, 47, **48,** 49, 173
Phasmida (*see Carausius*)
Phenylalanine, 125
Phosphates,
  and moulting, 249ff.
  and parathyroids, 142, 251ff., 256
  balance of, *241*, 249ff., **247**
  in blood, *254*, *255*
  metabolism of, 142, 240, 249
Phospholipids, 43, 187
Phosphoric hexose esters, 197, 250
Phosphorus turnover, 117
Phosphorylation, 177, 196ff.
Physiological colour change (*see* Colour change)
Pigeon's milk, 130
Pigment granules, 73ff., **75,** 77, 79ff., 82ff., 108
  black, 74, between **82** and **83,** 83, 97ff., *98*
  blue, 83
  concentration of, 73ff., 79, 83, 88ff.
  dispersal of, 73ff., 79, 83, 91ff.
  in epidermal cells, 74ff., **75,** 158
  in mesodermal cells, 102
  in retinal cells, 77ff., **78, 81**
  movements of, 73, 74, 80, 82ff.
  red, 74, face **82,** 83, 86ff., *98*
  reflecting, 83
  under pressure, 74
  white, 77, 83, 94ff., *96*
  yellow, 83
  yellow-green, 74, **75**
  (*see also* Chromatophores)
Pigment-concentrating hormone of *Penaeus*, **90**
Pigmentary effectors, 56, *71*, 73ff., *87*, 107ff., 152ff.
Pineal organ (*see* Epiphysis)
Pitocin, 237
Pitressin, 237
Pituitary body, **34, 36, 48,** 245
  anterior lobe of, 40ff., 40fn. (*and see* Adenohypophysis)
  extracts of, **104,** 199
  posterior lobe of, 33ff., 104 (*and see* Neurohypophysis)
Pituitary gland, **42**

Pituitrin,
  and calcium, *245*, 246, 249
  antidiuretic fraction, **210,** 211
  oxytocic fraction, **68**
Plant hormones, 2, 3
Plasmosol phase, 74
Platyhelminthes (flat worms), 12
Plecoptera (stone flies), 30
Pleuronectidae (flat fish), 83, **110**
Pores, ultramicroscopic, and ADH, 233, 235, 239
Porifera (sponges), 4, 167
Post-commissure organs, **24,** 25, 29, **90**
Potassium, K$^+$ (*see* Ions)
Pouch, from fundus of stomach, 119, **121, 122**
  from pylorus, 119, 120
Precursors of hormones, 91, 140
Pregnancy (and gestation), 64, 150, 151, 152
Preoptic nucleus, 33
Pro-, meso-, and meta-adenohypophysis, 40
Progesterone,
  actions of, 64, 128ff., *129*, 152, 153
  endocrinokinetic control of, *133*, 150ff., *157*, 162
  source of, 50
Prolactin, LSH, 128, *129*, 130, 150, 152, 153, *157*, 160, 161
Pronephric ducts, 52, 227
Protective, coloration, 70, 84
  responses, 259
Protein,
  anabolism, 199, 201
  catabolism, 205, 249, 250, 251
  contraction of molecules, 80, 82
  digestion of, 125
  in moulting crabs, **202,** *204*
  metabolism, 10, 11, 135, 189, *190*, 199ff., *200*, **202,** 252
  of chromatophores, 74
  restraint of catabolism of, *190*, 199ff., *204*, *254*, 257
  synthesis, *190*, 203, 205, 249, 252, 253, *254*, *255*
Prothoracic gland hormone (*se* Moult-promoting)
Prothoracic glands,
  and metabolism, 183ff., *190*, 195, *241*, 251
  as source of ecdysone, *8*, 18, **30,** 38
  endocrine control of, *133*, 135ff., *255*, 258
Prothoracotrophin, 12, 136, **137,** *156*, 184, 258 (*see* Intercerebrum, for source)
Protocerebrum, of Arthropoda, *22*, **24,** 25, **30,** 31
Protochordata, 47, 173, 174
Proventriculus of birds, 122
Pupae, in diapause, **137,** 184, 185

Reflecting cells, 77
Regeneration, *8*, 11, 135
Release mechanisms for secretions, 258
Renal calculi, and Ca metabolism, 243
Reproduction, 148ff., 151ff.
Reptilia, 33, **36** (*see also* Chelonia, Lacertilia *and* Ophidia)
  and kinetic hormones, 74, 83, 85, 94, 107, 109, **110,** 124
  and metabolic hormones, *169*, 193, *208*, 215, 237
Respiration, *8*, 10
  aerobic, 209
  and cytochrome *c*, 182
  cyanide stable, 182
  decreased rate of, 168, *169*, **171,** 178ff.
  increased rate of, *8*, 168ff., *169*, **172**
Respiration-inhibiting hormone, **178,** 179, **180,** *254*

Respiratory accelerator hormones, 168ff., *169*, *254*, *255*

Respiratory inhibitor hormones, 178ff., *254*

Respiratory quotient, 180

Responses, graded, 154

Retina, **24**

Retinal cells, contractile fibres in, *71*, 79, 80, **81**

- distal, *71*, 74, 77ff., **78,** 80ff., **81,** 108
- proximal, 77, 79

Retinal-dark, and -light-adapting hormones, 80ff., **81**

Retinal-pigment-concentrating and -dispersing hormones, RPCH and RPDH, **78,** 79ff., 108, *156*

Retinula cells, 74, **81**

Retrocerebral system of insects, 33

Rhabdome, **81**

Rhythm, diurnal, in Ca metabolism, 242

- diurnal, in pigment cells, 80ff., 85, 86, 93, 99, 103, 259
- of nocturnal activity, 69
- of muscle contractions, face **62,** 63
- of secretion, 116, 144
- tidal, 85, 259

Ring-gland, of Diptera, 135, 195

Ringer's solution, 59, face **62,** 63, **213,** 233

Rodentia (*see Cavia and Rattus*)

Saccus vasculosus, 41

Saline, hypertonic, 228, 239

- injections, *14*, 37, **148,** 212, **224**
- medium, 218, **232,** 233 (*see also* Ringer's solution)

Salinity, changing, 215, 227

- excessive, 212, 218

Salivary glands, of Cephalopoda, *22*, 38ff., 73, 116, *208*, 230

- of Mammalia, 117, 216

Salt, NaCl, concentration in blood, 143, 206, *208*, 209ff., 225ff.

- excretion of, 13, **213, 214,** 218, 218fn., 220, 258
- injection of, *14*, **92, 175,** 191, **224**
- in medium, **224, 232**
- reabsorption of, 206, **211,** 212, **214,** 218, 235
- uptake, **210,** 211 (*see also* Electrolyte balance *and* Ions)

Seawater, **92,** 212, 218, 226, 236

- hypertonic, 37, 207, 236
- hypotonic, 237
- migration from, 206, 212

Secretagogues, 5, 117, 119, 124

Secretin, action of, 1, *8*, *118*, 119, 120, **120,** 122ff., 127

- control of secretion of, 57, 123, **123,** *156*, 253
- source of, 45, *46*, 56, 64, 123ff.

Secretion,

- by nerves (*see* Neurosecretion)
- inhibition of, 117, 126ff.
- of acid, *118*, 119ff., **120, 122,** 127, 153, 253
- of bicarbonate, **120,** 122ff., **123,** 253
- of enzymes, 115, 116, 117, *118*, 124ff., **125,** 127
- of hormones, *q.v.*
- phases of, 20, face **22,** between **22** and **23, 32,** 52

Secretory cells (*see* Endocrine *and* Exocrine secretory cells)

- giant, **32**

Sensitivity, threshold of, 154

- specific variation in, 235

Sex-differentiation,

- in pigmentation of *Uca*, 99
- in secondary characters, 149, 150, 151

Sinus gland,

- as storage organ, *22*, **24,** 25ff., **26, 27,** 33, 35
- equivalent organ in *Ligia*, 102

- Sinus gland extracts, 59, **89**, **90**, 91, **92**, 94, 97, 178ff., 191, 221, 222, 248
- Sinus gland hormones (*and see* Eyestalk hormones)
  - chromactivating, *87*, 88ff., **89**, **90**, **92**, 94ff., *96*, 97ff., *98*, 108
  - control of secretion of, *156*, *254*
  - decreasing fat consumption, *169*, 187ff.
  - diabetogenic, *8*, 189ff., *190*, *192*, 257
  - diuretic, *208*, **220**, 220ff.
  - heart-accelerators, *58*, 59
  - moult-inhibiting, *q.v.*
  - respiration-inhibiting, *169*, 178ff.
  - restraining protein catabolism, *190*, 199ff., 203, *204*, *254*
  - retinal-light-adapting, *71*, 80ff.
  - storage of, 25ff.
- Sinus gland implants, 220, **220**
- Sinus gland, means of controlling, *156*, *254*
  - removal of, 80, 94, 178, *179*, **181**, 187, *188*, 189, *192*, 199, *200*, 203, *248*
  - sectioning nerve to, *192*, 257
  - structure of, **24**, 25ff., **26**
  - supplying kinetic hormones, *58*, *71*, 80, 81, *87*, 88ff., **89**, *96*, 97ff., *98*, 108
  - supplying metabolic hormones, *169*, 178ff., 189, *190*, *208*, 220, *241*, 247, *248*
- Skeleton, decalcification of, 243, 252
- Skin, absorption of ions by, 209ff.
  - glands, 117, *129*, 131
  - imbibition of water by, 206, 231, 232
  - impermeability in Reptilia and Mammalia, 207, 237
  - permeability to water in Amphibia, 230ff., **231**, **232**
  - reactions of isolated, **226**, 231
- Skin sensitivity to hormones, 231
  - ultramicroscopic pores in, 233, 239
- Sodium chloride (*see* Salt)
- Sodium ions, Na^+, 37, 206ff., *208*, **214**, *217*, 252
  - increase in blood, 209ff., **210**, **211**, 212ff., 221
  - decrease in blood, **213**, **216**, 218ff., *229*
- Sodium pump, 209
- Somatotrophin, STH,
  - control of uncertain, *157*
  - relation to insulin secretion, 256
  - stimulation of glucagon secretion, *133*, 142ff., **194**, 194ff., 199, *255*, 259
  - source of, *22*, *44*
- Sources of hormones, 2, 18ff., *22*, *46*, *51* (*and see* Endocrine glands *and* Endocrine secretory cells)
  - ectodermal, 18ff., *22*, 38ff., 44
  - endodermal, *46*, 46ff., face **48**, **48**, 119ff., 127, 139ff.
  - extracts of (*see* Extracts)
  - from nervous system, 18, 19ff., *22*, face **22**, 38
  - from neurosecretory cells *q.v.*
  - in Cephalopoda, 21ff., *22*, **23**, 38
  - in Crustacea, *22*, 23ff., **24**, **26**
  - in Insecta, *22*, between **22** and **23**, face **23**, 29ff., **30**, **32**, 39, **62**
  - in Vertebrata, 18, 19, face **22**, *22*, 33ff., **34**, **36**, 40ff., **42**, *44*, 44ff., *46*, face **48**, **48**, 50ff., *51*, **53**
  - location of, 12ff., *14*, 86, 109
  - mesodermal, face **48**, 50ff., *51*, **53**
- Sperm in fallopian tube, 65
- Starvation, 187, *188*, *200*, 205
- Stellate ganglion, 21, *22*, **23**
- Sterolic hormones, 50, 52

Stimulation of hormone secretion, 46, 56ff., 155ff., *156*, *157*, 253ff., *254*, *255*
  chemical, 57, 123ff., 125ff., 155, *156*, 253ff., *254*
  hormonal, 57, 115, 131ff., *133*, *157*, 158, 162ff., *254*, *255*, 258 (*and see* Endocrinokinetic hormones)
  mechanical, 56, 119ff., 155, *156*
  nervous, 38, 57, *156*, *157*, 158, 160ff., *254*, 257ff.
Stomach, 5, 44, 45, 119, **120,** *156*
  glands (gastric), *118*, 119ff., 126
  pouches, 119ff., **121, 122**
Stomatogastric system of insects, **30,** 39
Stomatopoda, 25, 29
Stomodaeum, **30,** 33, 40, **48**
Storage-and-release organs for neurosecretion, 4, 20, *22*, 258
  in Crustacea, 23ff., **24, 26,** 28, 80, 188, 248
  in Insecta, **30,** 31ff., **32,** 61, **62,** 173, 203, 222
  in Vertebrata, 33, **34,** 35, **42,** 44
Stress, 167, 189, 195, 205 (*and see* Emergency)
  and ACH, 52, 144ff., **145**
  from asphyxia, 189ff., 192
  from haemorrhage, 11, 145
Suboesophageal ganglia,
  and diapause, *169*, 182ff., *254*, 257
  and motor activity, *58*, 69, 153
  and pigment dispersal, *71*, 75ff., **76,** *156*
  as source of hormones, *22*, between **22** and **23, 24,** 29ff., **30**
  endocrinokinetic action of hormone from, *133*, 135
  extract of, 223, **224**
Succus entericus, 126
Sugar, in blood (*see* Blood-sugars)
  in tissues, 189, 195, 197ff., 253
Sugar,
  in urine, 234 (*and see* Diabetes mellitus)
Sugar molecules, responsive to insulin, 197, **198,** 253
Supraoesophageal "brain" of Arthropoda, 28ff.
Supra-optic nucleus of hypothalamus, *22*, face **22,** 33, **34,** 35
Suprarenal body, 33, 68 (*and see* Adrenal medulla)
  cells of, 51
Suprarenal, gland, 38fn.
  tissue, *22*, 37
Sweat glands, *129*, 131, 216, 237
Sympathetic nervous system (*see* Nerves)
Syndrome, emergency, 67
Synergistic action of hormones, 150, 252, 256
Syrphidae (syrphid flies), 185

Teleostie,
  and kinetic hormones, 83, 94, 102, **106,** 106ff., 109, **110,** 139
  and metabolic hormones, *169*, 174, **176,** 193, 197, *208*, 212, 218, 226ff., 235ff., 243, 251
  sources of hormones in, *46*, 47, *51*, 51ff.
  use of mammalian hormones on, 212, 218, 243ff.
Temperature, effect on chromatophores, 85
Terminal medulla of optic lobe, **24,** 25, **26,** 28
Terrestrial mammals and water, 237
Testis, 1, 4, 6, *8*, 149, 151, *157*
Testosterone, 6, *8*, 70, *133*, 149, 151, *157*
Tetany, muscular, and Ca lack, 244ff., 246, **247**

Tetrapoda, face **22**, 33, **36**, 40, *46*, 47, 49, 50, 51, *51*, 67 (*see also* Amphibia, Reptilia, Aves *and* Mammalia)
Thiouracil, 141
Thiourea, 233
Thirst, 37, 207, 239
Thoracic ganglia, **24**, **30**
Threshold, levels of sensitivity, 154
  values for hormone action, 249
  values for hormone stimulation, 256
Thymus gland, 47, **48**
Thyroglobulin, 140
Thyroid gland,
  and blood-P, *241*, 243, 244
  as source of thyroxine, 46, 47ff., face **48**(*a*), **48**
  cells of, 48ff., face **140**, face **141**
  endocrinokinetic control of, *133*, 139ff., face **140**, face **141**, *255*, 256 (*and see* TSH)
  extracts of, 174, **175**, **176**
  in Agnatha, 173ff.
  in Amphibia, 140, 174ff.
  in Aves, 177
  in fish, 139, 174, 189, *208*, 213ff., 227, 244
  in hibernation, 186
  in Mammalia, 140, **175**, **176**, 177, 187, 188ff., **194**, *208*, *241*, 243
  in Protochordata, 173
  morphogenetic effects of secretion, *8*, 12, 140, 257, 259
Thyroidectomy, difficulty of, 174, 177
  effect on blood-P, 250
Thyrotrophin, TSH,
  and iodine metabolism, 140ff.
  and parathyroid glands, 243, *245*, 246, 256ff.
  control of secretion of, 141, 149, *157*, 161
  endocrinokinetic action of, 12, 49, *133*, 139ff., face **140**, face **141**, 174, 177, 187, 188, 213, *255*, 259
  growth-promoting action of, 10, 142
  source of, *22*, 43, *44*
Thyroxine, action of, *169*
  in Amphibia, 175, 259
  in Chordata, 70, *169*, 173, 187, 188ff., *208*, 243
  in fish, 215, 227
  in Mammalia, **176**, 177, 195, 250
Thyroxine, and cretinism, 1
  and cycle of iodine metabolism, 140ff.
  and feed-back, 141, *157*
  and metamorphosis, *8*, 12, 259
  and parathyroids, 243, 256
  precursors of, 49, 140, 141
  secretion stimulated by TSH, *133*, 139ff., *255*
  source of, *46*, 47, face **48** (*a*)
Tissues,
  and sugar supply, 189, 195, 197ff., 253
  embryonic, 182, 184
  enzymes of, 140
  hormone breakdown in, 59, 91, 140, 155, 184
  iodine cycle in, 140
  permeability changes in, 220, 225, 228ff.
  protein synthesis in, *190*, 249 (*and see* Protein)
  protection from diapause, 184ff.
  salt content of, 206, 207, 215
  water content of, 206, 226ff., 230, 237, 239
Translocation, of calcium and phosphates, 250
  of fats, *255*
Tritocerebral, commissures, **24**, 28, 29, 80, **90**, 91, **92**, 94
  lobe, 25

Tritocerebrum of Arthropoda, **24,** 25, 28, **30**
Trophic hormones, 9ff., 132 (*see also* Endocrinokinetic hormones)
Tropic hormones (*see* Trophic hormones)
Tryptophane, 125
Tyramine, *22*, 38, *71*, 73

Uca, chromactivating hormones of, *87*
  for black pigment, UDH and ULH, face **83,** *98*, 99
  for red pigment, URCH and URDH, **89,** 93, *98*, 99
  for white pigment, UWCH and UWDH, 95, *96*
Ultimobranchial bodies, *46*, 47, **48,** 49, *241*, 243ff., 251
  compared with parathyroids, 244, 256ff.
Ultra-violet light and Ca, 246
Urea, 227, 234
Ureters, separate collection of urine from, 238
Uric acid, 237
Urine, **214,** 231, **234,** 235, 237, 239
  hypertonic, 238, 239
  hypotonic, 206, 225, 227, 239
  output, **216,** *229*, **238**
Urochordata, 173
Urodela (*Necturus* and salamanders), 35, **36,** 41, 128, 193
Uterine glands, 128ff., *129*
Uterus, face **62,** 64, **65,** 151

Vagal nerve endings, 239
Vagus nerve, 45, 62, 64, 121, 123, 124, 125, 127
Vas deferens gland, *8*, 132
Vascular constrictor, 239 (*and see* Vasopressin)
Vascular hormones, 3, 4, 6, 11, 19, 20 *et seq.*
Vascular plexus, **36,** 41, **42**
Vascular plexus in cortex, **53**
Vascular system, 67
Vascular tissue, 119
Vasoconstriction,
  in Cephalopoda, 116
  in Vertebrata, **66,** 67, face **68**
Vasodilation, 66, face **68**
Vasopressin, ADH, *58*, 67, *157*, 159, 211fn., 230, 234, 239 (*see also* Antidiuretic hormone)
Venous plexus of pituitary, **36,** 41, **42**
Ventral gland, 30, **30,** *133*, 135
Vertebrata, 2, 7, *8*, 11, 12 (*and see* Agnatha, Amphibia, Aves, Elasmobranchii, Fish, Mammalia, Reptilia *and* Teleostei)
  and balance of Ca and P, 240, *241*, 243ff., **247,** 249, 250ff.
  and balance of electrolytes and water, *208*, 209ff., **214, 216,** 220, 225ff., 230ff., **238**
  and chromatophores, 83, 86, *87*, 94, 102ff., **104, 106,** 109, **110**
  and control of endocrine glands, 132, *133*, 139ff., **145,** *156*, *157*, 159, 160ff., *254*, 255
  and control of metabolic hormones, 253, *254*, *255*, 257, 259
  and exocrine glands, **66,** 115, 116, 117, *118*, **120, 122, 123, 125,** 128ff., *129*, 130ff.
  and intermediary metabolism, 185ff., 187, 188, 189, *190*, 191ff., 195ff., **196,** 205
  and muscles, 56, *58*, 59, 61ff., 63ff., 70
  and respiration, 167, 168, *169*, 173ff., **175, 176,** 185
  sources of hormones in (*see* Sources)

Vertebrata cold blooded, 5, 44, 63
  and kinetic hormones, 82, 122, 124, 144, 149, 155
  and metabolism, 173, 193, 253
Vertebrata, lower, 45, 47, 74, **110**, 127
Visceral arches, **48**, 49
Visceral muscles, 57ff.
Visceral nervous system, **30**
Vitamin D, 246
Viviparous development, 151

W (*see* Melanophore concentrating hormone)
Water, antidiuresis, 228ff., **238**
  balance, *8*, 10, 143, 168, 206, *208*, **214**, 219ff., **220**, **232**, 239
"Water-balance principle", 230
Water, diuresis, 143, 201, 207, *208*, **214**, 219ff., 223, **224**, 225ff., 240, 257
  excretion, 222, 223, *229*
  flux through skin, affected by hormone, 233
  loss, 228, 231
  reabsorption, 230, **234**, 235, **236**, 237
  retention, 223, 246
  uptake, 220ff., **223**, **224**, **226**, 228, 230ff., **231**, 239
Water-loaded, rats, 227, 228, *229*
  tissues of fish, 227
Weismann's ring (gland), in Diptera, 135, 195

Xanthophores, between **82** and **83**, 83
X-organ, confused use of name, 28 (*see* Ganglionic-X-organ *and* Hanström's sensory-pore organ)

Y-organ in Crustacea, *8*, 18, 38
  and metabolic hormones, *190*, 199, 203, *204*, 222, 240, *241*, 242ff., 249, 251
  endocrinokinetic control of, *133*, 134ff., *254*, 258
  extract of, **242**

Zona fasciculata, **53**